

A decision support tool to facilitate the development of a
pharmacovigilance system within the context of the
Medicine Patent Pool.

by
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Declaration

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Abstract

In the modern-day healthcare landscape, innovative drug manufacturing and distribution systems have become increasingly prevalent, especially in resource limited settings (RLS). One such innovative system is the Medicines Patent Pool (MPP), which seeks to increase the availability and affordability of treatments for HIV, TB, and Hepatitis C by making available specific patents to generic pharmaceutical manufacturers. However, the implementation of the MPP has led to the emergence of certain challenges with respect to inadequacies in drug manufacturing and distribution, which affect the pharmaceutical value chain and drug safety monitoring (Burrone, 2016). The context within which the MPP was launched thus call for effective drug safety monitoring and pharmacovigilance (PV) systems. PV is the science and application of the detection, assessment, and monitoring of adverse drug reactions (ADRs) in response to drugs, with the objective of minimising drugs risks through the effective and efficient reporting of ADRs (WHO, 2002b).

This research inquiry is thus aimed at addressing the lack of an effective PV system in the environments covered by the MPP; such a system must also consider the context of RLS and the disease burden of HIV, TB and Hepatitis C (which are referred to as the MPP drug provision systems) by proposing a decision support tool that facilitates the development of context-specific PV systems. A system engineering approach was thus followed to contextualise and address the development of said tool.

Initially, systematic literature reviews were conducted to develop a challenges landscape pertaining to four niche factors, namely, (i) traditional PV systems, (ii) the MPP, (iii) HIV, TB, and Hepatitis C, and (iv) RLS within the context of the pharmaceutical value chain. This challenges landscape was developed to gain a systems perspective understanding of the various challenges that a context-specific PV system would have to address.

Building on the insights gained from this challenges landscape, a requirement specification was developed for a context-specific PV system within the context of the MPP drug provision systems. Additional systematic literature reviews focused on the four factors listed above, within the context of identifying the requirements that these factors call for in a drug safety monitoring system. Furthermore, a verification process was conducted with subject matter experts (SMEs) to evaluate the identified requirements. Building on these findings, a requirement specification was drafted to guide the development of a decision support tool.

In order to address the requirement specification, possible intervention strategies were identified. The identified intervention strategies were then synthesised to develop components for an alternative, context-specific PV system. Based on these findings, a decision support tool that would facilitate the development of a context-specific PV systems was developed. This decision support tool is referred to as the *Customised Vigilance System Implementation Tool (CVSIT)*. Through validation processes it was found that the CVSIT is a robust, adaptable tool, that provides a customized strategy based on a specific projects profile. It was validated by means of (i) a case study and (ii) semi-structured interviews with SMEs to evaluate the applicability and practicability of the tool.

Opsomming

In die moderne gesondheidsorglandskap het innoverende medisynevervaardigings- en verspreidingsstelsels al hoe meer algemeen geword, veral hulpbronbeperkte omgewings. Een so 'n innoverende stelsel is die *Medicine Patent Pool* (MPP); die MPP het die doel om die beskikbaarheid en bekostigbaarheid van behandeling vir MIV, TB, en Hepatitis C te verbeter deur patente aan generiese farmaseutiese vervaardigers vry te stel. Maar, die implementering van die MPP bring sekere uitdagings met betrekking tot die gebreke in die vervaardiging en verspreiding van geneesmiddels na vore wat die farmaseutiese waardeketting en die monitering van medisyneveiligheid beïnvloed (Burrone, 2016). Die konteks waarin die MPP van stapel gestuur word, vereis doeltreffende monitering en geneesmiddelbewaking stelsel. Geneesmiddelbewaking is die wetenskap en toepassing van die opsporing, evaluering en monitering van nadelige reaksies op medikasie, met die doel om die risiko's van medisyne tot die minimum te beperk deur die effektiewe en doeltreffende rapportering van nadelige reaksies op medikasie (World Health Organization, 2002).

Hierdie navorsingsondersoek is daarop gemik om die gebrek aan 'n effektiewe PV-stelsel in die omgewings van die MPP, wat die konteks van hulpbronbeperkte omgewings en die siektelas van HIV, TB en Hepatitis C, aan te spreek deur die ontwikkeling van 'n besluitsteun hulpmiddel wat die ontwikkeling van 'n effektiewe geneesmiddelbewaking stelsel fasiliteer. 'n Stelsel ingenieurswese benadering is gevolg om die probleem te kontekstualiseer en aan te spreek.

Aanvanklik is sistematiese literatuuroorsigte gedoen om 'n uitdagingslandskap te ontwikkel rakende die faktore van (i) tradisionele geneesmiddelbewaking-stelsels, (ii) die MPP, (iii) HIV, TB, en Hepatitis C, en (iv) hulpbronbeperkte omgewings binne die konteks van die farmaseutiese waardeketting. Hierdie uitdagingslandskap is ontwikkel om 'n oorsiggewende perspektief te verkry van die verskillende uitdagings wat 'n besluitsteun hulpmiddel in ag moet neem.

Aan die hand van die insigte wat uit die uitdagingslandskap verkry is, is 'n vereiste-spesifikasie ontwikkel vir die besluitsteun hulpmiddel wat die ontwikkeling van 'n effektiewe geneesmiddelbewaking stelsel in die konteks van die MPP-medisyneverskaffingsstelsels fasiliteer. Bykomende sistematiese literatuuroorsigte rakende die faktore van (i) tradisionele PV-stelsels, (ii) die MPP, (iii) HIV, TB, en Hepatitis C, en (iv) hulpbronbeperkte omgewings is ondersoek om vereistes te identifiseer wat hierdie faktore vereis van 'n geneesmiddelbewaking-stelsels. Verder is 'n verifikasieproses met vakkundiges uitgevoer om die geïdentifiseerde vereistes te evalueer.

Ten einde die vereiste-spesifikasie aan te spreek, is moontlike intervensiestrategieë geïdentifiseer. Intervensiestrategieë is daarna gesintetiseer om komponente vir die besluitsteun hulpmiddel te ontwikkel. Gegewe hierdie bevindinge, is 'n besluitsteun hulpmiddel ontwikkel wat die ontwikkeling van 'n effektiewe geneesmiddelbewaking stelsel fasiliteer. Die besluitsteun hulpmiddel word genoem die *Customised Vigilance System Implementation Tool* (CVSIT). Deur 'n validasieproses is bevind dat die CVSIT 'n aanpasbare instrument is,

aangesien dit 'n unieke strategie ontwikkel gebaseer op 'n spesifieke projek se profiel. Die CVSIT is gevalideer deur (i) die toepassing van 'n gevallestudie en (ii) semi-gestruktureerde onderhoude met vakkundiges te voer om die toepasbaarheid en bruikbaarheid van die hulpmiddel te evalueer.

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Lastly all glory to my Lord and savior who was my guiding light throughout this study.

For I know the plans I have for you,” declares the LORD, “plans to prosper you and not to harm you, plans to give you hope and a future. Jeremiah 29:11.

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List of Abbreviations

ADR	Adverse Drug Reactions
ART	Antiretroviral Treatment
ARV	Antiretroviral Drugs
BCAP	Clinical Access to Bedaquiline Programme
CEM	Cohort Event Monitoring
CVSIT	Customised Vigilance System Implementation Tool
GDP	Good Distribution Practices
GMP	Good Manufacturing Practices
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Practitioner
ICT	Information Communication Technologies
IPAT	Indicator-Based Pharmacovigilance Assessment Tool
ISoP	International Society of Pharmacovigilance
HIV	Human Immunodeficiency Virus
MCC	Medical Control Council
MDR-TB	Multi-drug Resistant Tuberculosis
MPP	Medicine Patent Pool
MRA	Medicine Regulatory Authorities
PDR	Patient Direct Reporting
PV	Pharmacovigilance
PVCCL	Pharmaceutical Value Chain Challenges Landscape
R&D	Research and Development
RLS	Resource Limited Settings
SAHPRA	South African Health Products Regulatory Authority
SME	Subject Matter Experts
SMS	Short Message Services
TB	Tuberculosis
TSR	Targeted Spontaneous Reporting
UMC	Uppsala Monitoring Centre
VBA	Visual Basic for Applications
WHO	World Health Organisation
XDR-TB	Extreme drug resistant TB

Table of Keywords

Keyword	Definition within the context of this research inquiry	Reference Page
Customised Vigilance System Implementation Tool (CVSIT)	This is a decision support tool that aims to assist drug provision projects with developing a customised implementation plan for a Vigilance System based on the projects' vigilance profile.	138
Medicine Patent Pool (MPP)	The MPP is an innovative platform that improves access to communicable disease treatments for HIV, Hepatitis C and TB in low- and middle-income countries through sharing technologies and patents.	1
MPP drug provision systems	These systems consist of different practices in a pharmaceutical value chain, such as drug manufacturing, distribution, and quality monitoring within the context of the MPP and considering the environment of RLS. Within the context of this research this is one of the Niche factors	2
Niche factors	Niche factors are factors that specifically affect MPP drug provision systems and that should be taken into account when developing a context-specific PV system. The four niche factors are (i) traditional PV systems, (ii) the MPP, (iii) HIV, TB and Hepatitis C, and (iv) RLS.	7
Pharmaceutical value chain challenges landscape (PVCCL)	This provides an overview of the different challenges associated with the Niche factors within the context of PV systems and drug safety monitoring.	67
Pharmacovigilance (PV)	PV is a form of drug safety monitoring applied for the detection, assessment and monitoring of adverse drug reactions after drugs have been licenced for use.	1
Profile-intervention mapping tool	This is the third dimension of the CVSIT; it refers to the background logic section of the tool, which maps the vigilance profile against the Vigilance System Component-Intervention Index.	137
Resource limited settings (RLS)	RLS are defined as environments where the capability to provide care to life-threatening illnesses is limited to the provision of basic resources, i.e. financial, academic, and human	1
MPP disease burden	This is a niche factor, which refers to the group of diseases addressed by the MPP, namely HIV, TB and Hepatitis C.	42
The Vigilance System Component – Intervention Index	The Vigilance System Component – Intervention Index outlines the foundational features of the decision support tool, by providing an overview of the various Vigilance System components and subsequent interventions	115

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Keyword	Definition within the context of this research inquiry	Reference Page
Vigilance implementation strategy	The fourth dimension of the CVSIT is the user output level and it provides the user with the customised implementation strategies for a Vigilance System for a specific drug provision project.	137
Vigilance profile assessment	The first dimension of the CVIT is the user input section, as the user needs to complete questions related to the specific project, patients, human resources, and technology resources.	137
Vigilance System	The Vigilance System defined as a context-specific PV system for MPP drug provision systems that assists with the effective and efficient reporting of ADRs through the development of a decision support tool	111
Traditional PV systems	This refers to the current practices and process of PV systems within the universal healthcare environment.	3

Chapter 1: Introduction

In this chapter an overview of the research inquiry is provided. It begins with an introduction to the background of the research, followed by the research problem statement, aim, and objectives. Then the scope and limitations of this study are presented. The research strategy, which includes the methodology and validation approaches are subsequently discussed, as well as the expected outcome of the study and an outline of the thesis structure.

1.1 BACKGROUND

Pharmacovigilance (PV) is a form of drug safety monitoring that is defined as the science and application of the detection, assessment and monitoring of adverse drug reactions (ADRs) after drugs have been licenced for use (WHO, 2002b). The key objective of a PV system is to effectively and efficiently report and monitor ADRs in an attempt to minimise risks. In addition, the identification and evaluation of previously un- or underreported ADRs is also a vital part of such a PV system (Metha *et al.*, 2017).

In the modern-day healthcare landscape, there has been a significant shift in the healthcare trends around the world that calls for innovative drug manufacturing, distribution and surveillance monitoring. According to Rohrbach (2017), due to the growing demand for healthcare, combined with the shift in focus from treatment to prevention, pharmaceutical companies are under pressure from governments and consumers to reduce prices and improve the value of therapies. Other stakeholders, such as the World Health Organisation (WHO), are also contributing to this pressure (Rohrbach, 2017). Furthermore, it is perceived that the epidemic of communicable diseases in resource limited countries further contributes to the pressure pharmaceutical manufacturing companies are experiencing from stakeholders to ensure an affordable drug supply. These factors, in combination with strict drug patent laws, are challenging affordable drug supplies in these countries (Modell, 2003).

In order to address the unavailability of drugs with reference to certain populations, the UNITAID Medicine Patent Pool (MPP)¹ was established in 2010 to improve access to treatment of Human Immunodeficiency Virus (HIV), Tuberculosis (TB), and Hepatitis C by allowing access to specific drug patents (Medicines Patent Pool, 2010). The aim of the MPP is to increase the rate of manufacturing and decrease the prices of specific drugs, i.e. drugs related to HIV, TB and Hepatitis C, in an attempt to increase the availability of these drugs to those who are affected (Perry, 2012).

The fact that numerous manufacturers could be utilised through the MPP to produce drugs intensifies the need to monitor drug quality and the consistency of quality across manufacturers, and thus highlights the need for effective drug safety monitoring, by means of PV systems, within this context. Furthermore, research has shown that certain challenges arise as a result of the implementation of the MPP, often with respect to drug manufacturing and

¹ MPP is an initiative that allows any manufacturer to access the available patents and to manufacture drugs, thereby aiming to decreasing the lead time and costs associated with these drugs.

distribution systems in these developing countries, which affects the pharmaceutical value chain and drug monitoring (Burrone, 2016). These challenges are attributed to inadequate local drug manufacturing and distribution systems, which often face the additional challenge of limited resources (Burrone, 2016).

In literature it has been argued that there are challenges in the PV system of developing countries that necessitate a change in the system (Metha *et al.*, 2017). In a study done by Allen (2014) the development of context-specific adverse drug monitoring and reporting guidelines and/or tools were highlighted in order to improve the effectiveness of ADR detecting, and monitoring within niche environments (Mehta, Allen, *et al.*, 2014). Thus, the need for context-specific considerations within PV systems have been highlighted, however the necessary tool and guidelines to facilitate such a system is found to be lacking (Mehta, Allen, *et al.*, 2014; Wilbur, 2018; Justo *et al.*, 2019).

Furthermore, contributing challenges have been identified when addressing PV in the context of (i) innovative drug manufacturing and distribution – such as the MPP, (ii) diseases burden associated with the MPP, and (iii) resource limited settings (RLS). This reaffirms that a proposed context-specific PV system should incorporate these factors by considering *MPP drug provision systems* a phrase referring to drug systems that consist of different practices in a pharmaceutical value chain, such as drug manufacturing, distribution, and quality monitoring within the context of the MPP, and by considering the environment of RLS.

The outline provided above highlights the need for alternative context-specific PV systems that take into consideration the context of MPP drug provision systems, as well as the entire pharmaceutical value chain.

1.2 PROBLEM STATEMENT, AIM AND OBJECTIVES

In this section the problem identified in the real-world situation is expressed, as well as the aim and the objectives of the research inquiry.

1.2.1 Problem statement

Innovative modes of drug manufacturing and provision practices, such as the MPP, are emerging globally, especially in RLS. Challenges experienced as a result of these emerging practices highlight (i) the inadequacy or lack of existing PV systems to support the unique PV needs that such systems require, and (ii) the need to enable such settings to develop and deploy PV systems effectively and efficiently in order to support the drug provision and supply in such environments.

Thus, the problem that this research seeks to solve is the lack of a context-specific PV system that would address the needs called for by MPP drug provision systems when considering the effective and efficient reporting and monitoring of ADRs.

1.2.2 Research aim and objectives

The aim of this research inquiry is to contribute towards effective and efficient reporting and monitoring of ADRs, by developing a decision support tool that facilitates the development of context-specific PV systems within the context the MPP.

Five research objectives (RO), and a number of sub-research objectives, that support the above stated aim have been developed. The research- and sub-research objectives include:

RO1 Review the literature pertaining to the factors of (i) traditional PV systems, (ii) the MPP, (iii) the specific disease considered by the MPP (HIV, TB and Hepatitis C), and (d) RLS, in order to contextualise the research problem under consideration, namely, the fact that traditional PV systems are inadequate in supporting the unique needs and challenges brought on by these factors.

RO2 Develop a challenges landscape related to the factors of (i) traditional PV systems, (ii) the MPP, (iii) HIV, TB and Hepatitis C, and (d) RLS in order to gain an understanding of what challenges any alternative, context-specific PV system will have to address. The sub-objectives related to this RO2 include:

RO2.1 Conduct systematic literature reviews to identify the challenges associated with each of the factors as stated above;

RO2.2 Identify and define possible relationships between the identified challenges and the pharmaceutical value chain;

RO2.3 Synthesise the challenges and the identified relationships to develop a challenges landscape that will support the development of a proposed alternative, context-specific PV system.

RO3 Develop a requirements specification that will guide the development of a decision support tool, drawing on the findings from RO1 and RO2. The sub-objectives related to this RO3 include:

RO3.1 Conduct systematic literature reviews pertaining to (i) traditional PV systems, (ii) the MPP, (iii) HIV, TB and Hepatitis C, and (d) RLS, to identify any additional requirements that these factors would call for;

RO3.2 Consider the developed challenges landscape as described in RO2, with respect to the identified requirements specification; as per RO3.1, to determine if additional requirements should be considered;

RO3.3 Synthesise the requirements identified in RO3.1 and RO3.2 to develop a combined requirements specification that will guide the development of a decision support tool; and

RO3.4 Conduct a verification process to authenticate the developed requirements specification as stated in RO3.3.

RO4 Develop a decision support tool that facilitates the development of a context-specific PV systems within the context of the MPP. The sub-objectives related to this RO4 include:

RO4.1 Identify possible intervention strategies that would address the requirements specification as discussed in RO3;

RO4.2 Synthesise the intervention strategies identified in RO4.1 to develop the foundational features of the decision support tool;

RO4.3 Develop the detailed decision support tool; and

RO4.4 Validate the developed decision support tool to evaluate the applicability and practicability of the developed tool.

1.3 SCOPE AND LIMITATIONS

This study is limited to a particular ‘niche’ environment, as it developed for the context of MPP drug provision systems and thus specifically focusses on the contexts related to PV and the MPP; and, this includes RLS and specific disease burdens addressed by the MPP, namely HIV, TB and Hepatitis C.

This research study thus will consider the MPP drug provision system and the challenges that are often associated with it. These challenges are mostly attributed to inadequate drug manufacturing and distribution systems. Once the challenges have been identified, it will be determined how these challenges affect the pharmaceutical value chain and subsequently the drug monitoring process. Similarly, challenges associated with the contexts of RLS and specific disease burdens addressed by the MPP, namely HIV, TB and Hepatitis C, will be identified and evaluated to determine how these challenges in-turn affect drug safety monitoring. The research also considers the challenges associated with traditional PV systems, as any proposed PV system should ideally address such challenges, or at least not amplify them. Once the challenges have been identified and the relevant literature has been reviewed, a requirements specification is developed that guides the development of a decision support tool that facilitates the development of context-specific PV systems within the context the MPP.

1.4 RESEARCH STRATEGY

This section will provide an overview of the research strategy and the verification and validation approaches that were followed. Furthermore, the description of the research products considered in this research inquiry is also provided.

1.4.1 Research methodology

In order to address the research aim - to contribute towards effective and efficient reporting and monitoring of ADRs, by developing a decision support tool that facilitates the development of context-specific PV systems within the context the MPP - a systematic research approach is required that allows for a structured approach to deal with complexity and the interrelatedness of components, in order to develop an appropriate solution for the complex context of PV. Thus, for this research inquiry a systems engineering approach was adopted as overarching research approach.

Systems engineering is defined as an interdisciplinary approach that facilitates with transforming of operational needs into system-level solutions that satisfies customers’ expectations (Blanchard and Fabrycky, 1998; United States Government, 2001; International Council On Systems Engineering (INCOSE), 2017). The systems engineering approach is thus

a comprehensive, iterative problem-solving technique that is used to translate needs and requirements into a system solution (United States Government, 2001).

The system engineering approach consists of four phases, namely: (i) input identification, (ii) requirement analysis, (iii) functional analysis, and (iv) design synthesis (United States Government, 2001). Each of these phases has its own subsections, which is provided below, and an illustrative outline of this approach is depicted in Figure 1.1.

1.4.1.1 Input identification

The input identification phase entails identifying and giving context to the factors that influence the context of this research, i.e. the environment of the MPP drug provision system. Given the context of this dissertation, i.e. the MPP, a comprehensive input identification investigation was not required, as the context is clearly defined, and the following factors were taken into account during the development of the decision support tool that facilitates the development of context-specific PV systems. These factors include: (i) traditional PV systems, (ii) the MPP, (iii) HIV, TB and Hepatitis C, and (iv) RLS. For the purpose of this research inquiry, these factors are referred to as the *niche factors*. During the input identification process, literature was consulted to contextualise these factors. Furthermore, to ensure that the proposed solution effectively addresses these factors, the challenges faced when addressing each of these niche factors in the context of drug safety monitoring was identified and evaluated. Subsequently, the identified challenges were synthesised to develop a challenges landscape pertaining to the context of MPP drug provision systems.

1.4.1.2 Requirement analysis

In accordance with the systems engineering process, once the inputs, i.e. niche factors and relevant challenges, had been identified, the requirements that will guide the development of the decision support tool could be specified. For this specific research inquiry, the requirement analysis phase entailed determining what requirements each of the niche factors would respectively call for in a context-specific PV system. These requirements were identified and determined by consulting the literature and the challenges landscape that was developed during the input identification phase. A requirements specification was thus developed for each of the four niche factors, and to evaluate the significance of these requirement sets, a verification process was conducted with a number of subject matter experts (SMEs). The verified requirements specification was used to guide the development of the decision support tool.

1.4.1.3 Functional analysis

The functional analysis phase entailed identifying intervention strategies that would best address the requirements specification developed during the requirement analysis phase. These strategies were identified by consulting the literature, referring to the requirements specification developed during the requirement analysis phase, observing real-world phenomena, and conducting interviews with SMEs. The identified intervention strategies were synthesised to develop an index that outlines the foundational features of the decision support tool.

1.4.1.4 Design synthesis

The final phase in the systems engineering approach is divided into two subphases namely subphase A, and subphase B. Subphase A focused on the operationalisation of the index that

outlines the foundational features by developing a decision support tool that facilitates the development of context-specific PV systems within the context the MPP. This tool, referred to as the *Customised Vigilance System Implementation Tool (CVSIT)*, is a decision support tool, that aims to facilitate the assessment of the profile of the drug provision project with regard to context of the project, the target patients group, the human resources availability, and the technology availability. And to then subsequently provide the user with a customised implementation strategy that outlines the required system components and interventions options to support an effective PV system within the context of the MPP. During sub-phase B, a validation process was conducted to evaluate the applicability and practicability of the developed tool, which is discussed in more detail in Section 1.4.2.

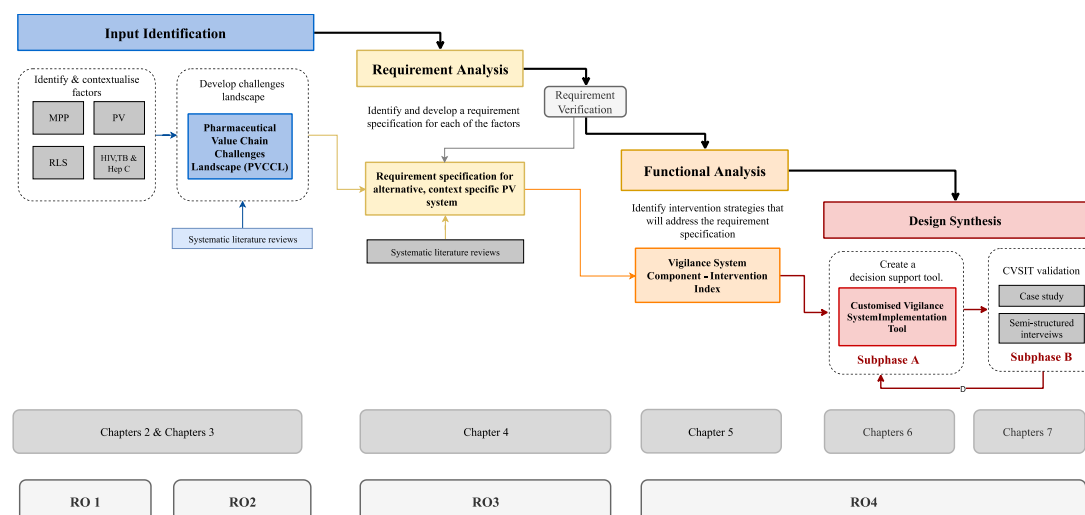


Figure 1.1: Schematic representation of the systems engineering research approach

1.4.2 Verification and validation approach

According to the IEEE-STD-610 Glossary of Software Engineering Terminology (1990), verification is the process of evaluating a system or component during a phase of development to determine if the system or component satisfies the conditions as stated during the initiation of said phase; whereas validation is the process of evaluation a product during the end phase of development to determine if the expectations and aims of the product is met (IEEE Standards Board, 1990).

As this research study is largely based on literature, verification and validation plays a significant role in applying the knowledge to real-world situations and gaining insights from subject matter experts' perspective. Thus, a verification and a validation process were conducted to evaluate research findings and outcomes at different phases of the research.

The verification process was conducted during Chapter 4, as shown in **Error! Not a valid bookmark self-reference.**, and entailed contacting SMEs to evaluate the requirement specification. The validation process was performed during the final phase of the systems engineering approach, i.e. the design synthesis phase, and was aimed at evaluating the decision support tool that was developed to assist with the effective and efficient reporting of ADRs in the environment of MPP drug provision systems. The validation process is documented in Chapter 7.

As mentioned, the verification process was performed with the aim of evaluating the developed requirement specification for a context-specific PV system. During the verification process, SMEs from different fields within the healthcare environment, i.e. pharmaceutical industry, PV industry, and academia, were consulted. The verification process involved contacting SMEs and providing the necessary documentation, i.e. pre-read² documents and questionnaires related to the developed requirements specifications, upon which they were required to provide feedback in the form of completion of the questionnaire. The aim of the verification was to evaluate the applicability of the identified requirements when considering the development of a decision support tool that facilitates the development of a context-specific PV system within the context of the MPP, and identify possible, additional requirements to take into consideration.

The validation process sought to evaluate the developed operational, decision support tool using two methods of validation, (i) conducting a case study, and (ii) conducting semi-structured interviews with SMEs. The first validation method is a retrospective case study in the field of drug safety monitoring to illustrate the operation of the tool. The aim of the case study was to evaluate whether the findings/ output of the tool corresponds with a real-world case study. The second method entailed conducting semi-structured interviews with SMEs. Similar to the previous method the aim was to evaluate the applicability and practicability of the tool, and furthermore to identify any possible weakness or refinements that should be made.

1.4.3 Research product terminology

The aim of this research inquiry is to contribute towards effective and efficient reporting and monitoring of ADRs, by developing a decision support tool that facilitates the development of context-specific PV systems within the context the MPP; however, to gain an understanding of the different possible research products that will be developed during this dissertation, the various research products and related findings are summarised in Table 1.1.

Table 1.1: Defined research products

Research product	Variations of research product	References
Decision support system	A decision support system is an information system (i.e. an organisational system designed for the collection, storage and distribution of data in a computer-based format) that assists with the decision-making process for business or organisational activities.	(Keen, 1980)
Tool	A tool is an instrument that is aimed at achieving a specified objective, through considering predefined inputs and providing a specified deliverable.	(Stinson, 2017; Hedreen, 2019)
Decision support tool	A decision support tool is a variation of a tool that incorporates techniques in order to assist with a decision-making process through considering predefined inputs.	(Stinson, 2017; Hedreen, 2019)
Index	An index serves as a representation /overview of various components that attribute to or should be taken into account when addressing a specific product / system.	(Collins, 2012)

² A pre-read document in the context of this research inquiry provides the validator with the required background information related to the specific component or system being evaluated. Thus, the pre-read document for the verification process provided information on the developed requirement specification and the pre-read documented used during the validation process provided context to the decision support tool.

Landscape	A landscape is a concept that considers the environment, and the attributes and characteristics of said environment	(Turner, Gardner and O'Neill, 2015)
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Considering these research products, it is envisaged that this research inquiry would focus on the development of a decision support tool, using complementary research products such as a landscapes and indexes.

1.5 THESIS OUTLINE

This thesis consists of eight chapters, and the respective chapters are outlined below.

Chapter 1: Introduction

In the first chapter, the background of the dissertation as well as the aims and objective for the research are described. Furthermore, an overview is given of the research approach and the validation process employed in this study.

Chapter 2: Niche factor contextualisation: Traditional pharmacovigilance systems

In this this chapter the input identification phase of the systems engineering approach is conducted by contextualising the first niche factor, i.e. traditional PV systems. This entails providing background information on the history of PV and the traditional PV process. In addition to the contextualisation of this factor, the challenges associated with traditional PV systems are identified through a systematic literature review. The identified challenges are investigated and synthesised to subsequently develop a PV challenges landscape. This chapter contributes towards RO1 and RO2.

Chapter 3: Niche factor contextualisation: Medicines Patent Pool, HIV, TB and Hepatitis C and resource limited settings

In this chapter, the input identification phase is continued by addressing the additional niche factors, namely, (i) MPP, (ii) the specific diseases , and (iii) RLS. Literature reviews pertaining to these three factors are conducted to provide context to MPP drug provision systems. As was the case in Chapter 2, a systematic literature review is conducted to identify challenges associated with these three factors in the context of a PV system, which is then synthesised to develop a challenges landscape related to MPP, specific disease and RLS. This challenges landscape is then combined with the challenges landscape developed in Chapter 2, in order to gain a comprehensive understanding of the challenges associated with the MPP drug provision systems, and this also contributes towards RO1 and RO2.

Chapter 4: Requirements specification development

In this chapter, RO3 is addressed by conducting the second phase in the systems engineering approach, namely, a requirement analysis, in order to identify the requirements each of the niche factors call for in a context-specific PV system. The requirements are identified by using the literature, consulting SMEs and incorporating the challenges landscape developed in the previous chapter.

Chapter 5: Vigilance System Component-Intervention Index development

Chapter 5 focuses on the third phase in the systems engineering approach, namely, the functional analysis. The focus here is on identifying intervention strategies that address the requirements specifications developed in Chapter 4, in order to develop an index based on

these findings that outlines the foundational features of the decision support tool. This chapter contributes towards RO4.

Chapter 6: Decision support tool development

This chapter further contributes towards RO4, as the focus is on developing the decision support tool that builds on the index developed during the functional analysis phase in Chapter 5. In this chapter sub-phase, A of the design synthesis phase of the systems engineering approach is conducted, which involves taking into consideration all the information obtained in the previous chapters to develop the decision support tool that facilitates the development of context-specific PV systems within the context the MPP.

Chapter 7: Validation process

In this chapter, sub-phase B of the design synthesis phase is completed, which is concerned with the validation of the developed decision support tool. The background, method and findings of the validation process of the developed tool are presented and discussed. The validation process entailed conducting a case study as well as semi-structured interviews with SMEs to evaluate the applicability and practicability of the developed tool. The results of the validation process are discussed, along with any changes and/ or refinements that were identifies and/or proposed during the validation process. RO4.4 is addressed in this chapter.

Chapter 8: Conclusions and future work

In this chapter, an overview of the research is provided as well as an evaluation of the research objectives. Furthermore, recommendations for future research is made. Chapter 8 concludes the research inquiry.

1.6 RESEARCH OUTPUT

The research outputs that were produced during research study are outlined below.

Journal article

A journal article, titled “Developing a challenges landscape relating to drug safety, provision and distribution in resource-limited settings for the case of HIV/AIDS”, was published in the South African Journal of Industrial Engineering (SAJIE) 2018, Volume 29, Issue 3. This article was produced from form the research documented in Chapter 3. Authors: Biancé Huysamen, Imke H. de Kock, and Louzanne Bam. The published article can be seen in Appendix A, Section A1.

International conference article

An international conference article titled, “The case for a niche pharmacovigilance system relating to drug provision and distribution in resource limited settings”, was accepted for publication in the Proceedings of the 25th ICE/IEEE International Technology Management Conference; 17th – 19th of June 2019, Sophia Antipolis, Nice, France. © 2019 IEEE. Authors: Biancé Huysamen, Imke H. de Kock, and Louzanne Bam. See Appendix A, Section A2.

1.7 CHAPTER 1 CONCLUSION

This chapter gives a concise background of the challenges associated with the inadequacy or lack of existing PV systems to support the unique needs that PV systems require within the

context of the MPP. The research aim and objectives for this research inquiry as well as the research strategy that will be followed to address the stated objectives are presented. The following chapter concerned with the input identification phase of the systems engineering approach, and the contextualisation the first niche factor, i.e. traditional PV systems, is thus presented in Chapter 2.

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Chapter 2: Niche factor contextualisation: Traditional pharmacovigilance systems

In this chapter, the processes related to the first phase of the systems engineering approach, namely, the input identification phase, are discussed with the goal of contextualising and investigating the first niche factor, traditional PV systems. In this chapter, traditional PV systems will be discussed with regard to the history and the processes relating to PV systems. Thereafter, the challenges associated with traditional PV systems will be investigated, discussed, and analysed in order to develop a challenges landscape pertaining to traditional PV systems that take into consideration the relationships between the identified challenges and the pharmaceutical value chain.

This phase of the research, and how it relates to the rest of the dissertation is shown in Figure 2.1.

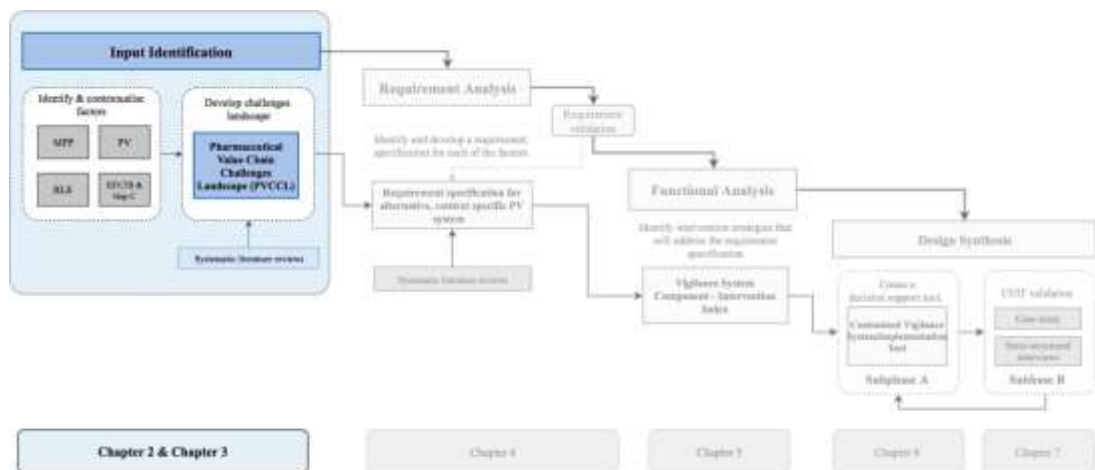


Figure 2.1: Systems engineering approach: Input identification

2.1 PROBLEM CONTEXTULISATION AND NICHE FACTORS

The input identification phase entails contextualising the research problem by identifying and investigating factors that have to be taken into account when addressing the research problem and the environment under consideration during the investigation; for the purpose of this research, this is the environment of the MPP drug provision system (United States Government, 2001). These factors have to be addressed when developing a decision support tool that facilitates the development of a context-specific PV system ³(United States Government, 2001).

³ For the purpose of this research inquiry a context-specific PV system is considered within the context of the MPP.

For the purpose of this research study, in-depth input investigation is not required as the environment under consideration during this study, i.e. MPP drug provision systems, constitutes that niche, context-specific factors would have to be taken into account. Thus, the process of identifying these factors were conspicuous, as these factors are distinctive to the environment of MPP drug provision systems. When considering this environment, it is evident that the following factors, (i) the MPP, (ii) HIV, TB and Hepatitis C, and (iii) RLS, are addressed when investigating the research problem. When considering the MPP drug provision systems, which refers to different practices in a pharmaceutical value chain within the context of the MPP and RLS, it is required that the context of the innovative drug provision systems, such as the MPP, are addressed as well as that the factor of RLS is considered. As stated in Section 1.1. through the MPP, numerous pharmaceutical manufacturing companies are provided the opportunity to manufacture drugs which established the need for effective drug safety monitoring systems in these environments, which are often associated with the challenges of having limited resource available (Burrone, 2016). Furthermore, when considering the MPP it is required that the disease burden addressed by the MPP is taken into consideration. Thus, it is required that a context-specific PV system for the environment of MPP drug provision systems, accounts for these diseases namely, HIV, TB and Hepatitis C. These diseases need to be addressed in isolation from the MPP as they could attribute to additional consideration that have to be taken into account when developing the proposed PV system.

As, the aim of this research inquiry is to develop a decision support tool that facilitates the development of context-specific PV systems, it is inevitable that the traditional PV systems also be considered as a factor during this dissertation. It is envisaged that the proposed context-specific PV system would be focused on rather transforming the traditional PV systems instead of transitioning to an innovative, new system. Thus, it is required that during this research inquiry the factor of traditional PV systems is contextualised and incorporated into the development of the proposed PV system.

Thus, due to the context of this research inquiry it is evident that there are four *niche factors*, (i) traditional PV systems, (ii) the MPP, (iii) the MPP disease burden namely, HIV, TB, and Hepatitis C, and (iv) RLS, that haven to be taken into consideration during the development of a decision support tool . Furthermore, it is relevant that when considering these factors, traditional PV systems, is firstly investigated as the aim of this study is foremost to consider a context-specific PV system, and thus the context of this factor firstly needs to be comprehended before considering the environmental context-specific factors. The niche factors, (i) MPP, (ii) HIV, TB and Hepatitis C, and (iii) RLS, are associated with the environment of the MPP drug provision system within which the context-specific PV system would have to function and thus the deduction can be made these three factors have to be taken into consideration within the context of the traditional PV systems.

However, to ensure that a context-specific PV system adequately address these niche factors, the challenges associate when considering each niche factor would have to be addressed in order to ensure that said system does not contribute to these challenges but possible assist in alleviating the challenges. Thus, during this research inquiry, systematic literature reviews pertaining to (i) traditional PV systems, (ii) the MPP, (iii) HIV, TB and Hepatitis C, and (iv) RLS, would have to be conducted in order to identify the challenges associated with these factors in the context of drug safety monitoring or PV. Furthermore, in order to gain a systems

perspective understanding of the challenges to address within the context of this research, i.e. MPP drug provision systems, a challenges landscape, pertaining to all the niche factors should be considered.

In this chapter the focus would be on contextualising the factor of traditional PV systems as it is imperative that the concept of PV and the process associated with this system is firstly investigated, as stated above. Thus, in the following section a background overview of PV systems will be provided after which the challenges associated with traditional PV systems will be investigated. Furthermore, these identified challenges will be synthesised in order to develop a challenges landscape pertaining to the challenges associated with traditional PV systems. This challenges landscape will form part of the development of the overarching challenges landscape which considers all the niche factors.

In the following chapter, a similar approach as discussed above will be conducted but considering the context of, (i) the MPP, (ii) HIV, TB and Hepatitis C, and (iii) RLS. The challenges landscape related to these factors will then be synthesis with the challenges landscape pertaining to traditional PV systems, developed during this chapter, to ultimately develop a challenges landscape for the context of MPP drug provision systems.

2.2 PHARMACOVIGILANCE SYSTEMS

As mentioned in Section 1.1 the WHO defines PV as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem” (WHO, 2015).

In this section, the history of PV is discussed as well as the process followed by a traditional PV system, when adverse effects or reactions to drugs are detected.

2.2.1 History of pharmacovigilance

PV started in 1961 after the Thalidomide disaster, when a large number of babies were born with phocomelia, a defect that caused their limbs to be deformed. Doctors and experts from across the world collaborated to investigate the cause of this defect and concluded that it was due to the off-label prescription of a mild sleeping pill, Thalidomide. This drug had been prescribed for the off-label use of morning sickness in pregnant women, although the effects of the drug on pregnant women were never verified in clinical trials (Schulz, 2001; Fintel, Samaras and Carias, 2009). Thalidomide was only taken off the market in 1962, by which time over 10 000 incidents of Thalidomide related disabilities had been reported (Fintel, Samaras and Carias, 2009). The Thalidomide disaster caused a shift in the healthcare industry and made the world aware that effective drug safety monitoring was essential in the healthcare system. According to the WHO, for a PV system to work effectively, it requires data collection from health practitioners, systematic monitoring and analysis of input data, especially in the case of new drugs that are rolled out (WHO, 2002b).

PV is aimed at improving patient safety with regard to medication but also contributes to monitoring and assessing different drug reactions and drug quality. Furthermore, to ensure effective monitoring, PV should be a continuous process throughout the pre- and post-authorization phases of a drug (WHO, 2002c). Although it is required for all drugs to go through a clinical trial, it is often the case that very little is known about the quality and safety of the drug (WHO, 2002c). For example, in order for a drug to be classified as safe to use, at

a 95% surety level, 30 000 patients would have to take part in a clinical trial (British Medical Association, 2006). When a new drug is rolled out, an effective PV system is thus of paramount importance, as all possible ADRs should be reported and investigated to insure the rapid detection of drug risks. Furthermore, PV systems must continuously be able to change and adapt in response to certain requirements within a setting (WHO, 2002c).

However, there are still many challenges with regard to drug monitoring, especially in developing countries (WHO, 2002c). From a study done on PV systems in South Africa, Uganda and India (2015), it was found that there are still barriers to be overcome, such as limited funding and a lack of training programs pertaining to PV for healthcare practitioners (HCP). Furthermore, with regard to the PV system in South Africa it was seen that, although legal requirements are in place, there is still a lack of effectively monitoring drug reactions to minimize risk factors (WHO, 2002c; Kadam *et al.*, 2015). The challenges associated with PV systems are discussed in detail in Section 2.3.

2.2.2 Pharmacovigilance process

The traditional PV system follows a process where ADR data is collected and analysed to determine if or what necessary drug safety interventions have to be taken when a drug is considered to be harmful (Meyboom *et al.*, 2002; Lindquist, 2004; Waller and Harrison-Woolrych, 2017). According to *An Introduction to Pharmacovigilance* (Waller and Harrison-Woolrych, 2017), a PV system must follow four essential steps: the process starts with the detection of possible hazards (i.e. ADRs) through (i) signal detection, followed by (ii) evaluation and investigation, then (iii) taking the required action, before (iv) considering possible methods of communication (Waller and Harrison-Woolrych, 2017). These steps are discussed in more detail in the following sections.

2.2.2.1 Signal detection

Signal detection refers to the detection and reporting processes of ADRs. In the context of spontaneous reporting⁴, a signal, which is defined by the WHO as information that has been reported about a possible unknown relationship between a drug and an ADR, needs to be generated by a series of reported cases, where the number of reported cases depends on the scarcity of the reported ADR (Waller and Harrison-Woolrych, 2017). A single case is usually not sufficient; only in very specific instances is one reported case of ADRs considered sufficient, for example, when a case of anaphylaxis⁵ is reported (Waller and Harrison-Woolrych, 2017). And thus, the strength of an effective PV system lies in the consideration of a series of reported cases, which is often lacking and/or challenging due to significant under-reporting. Since there are other methods of detection, a signal can also be defined as information that is obtained from various sources, including experiments and observations (Meyboom *et al.*, 2002; Waller and Harrison-Woolrych, 2017). Although passive reporting is often more common, the process of signal detection should ideally be an active process (Pohlman *et al.*, 2017; Waller and Harrison-Woolrych, 2017).

⁴According to the Uppsala Monitoring Centre spontaneous reporting refers to the voluntary process where patients or healthcare professionals report a suspected harm to their local or national PV centres.

⁵ Anaphylaxis is a severe allergic reaction that occurs within seconds of contact with the substance and can lead to death, i.e. peanut allergies (Scopus, 2019).

2.2.2.2 Evaluation and investigation

Two formal methods are used to evaluate the signals, namely, triage and impact analysis. Triage is most widely used by the WHO and entails the quick analysis of the most important features of a case, such as the seriousness and outcomes, in order to decide on the urgency of the case; impact analysis, in contrast, is a more quantitative method, which involves calculating two scores, viz., the evidence score and the public health score, to determine the overall priority of a case (Lindquist, 2007; Waller and Harrison-Woolrych, 2017).

When evaluating a signal, there are four key aspects to consider. Firstly the *causality* (in other words, does the balance of information support cause and effect), the *frequency* (in other words, how often is the effect or harm occurring), then the *clinical implications* (i.e., if the ADR is not serious, are there other effects that do call for further investigation) and lastly, *preventability* (i.e., are there any possibilities of preventing ADRs from arising) (Waller and Harrison-Woolrych, 2017).

The outcomes of such signal evaluation are often that further investigation is required; however, if the evidence supports the fact that immediate action is required urgently, confirmation is not necessary (Lindquist, 2004; Waller and Harrison-Woolrych, 2017). If no immediate action is required, signals are investigated further to obtain more information related to the drug and the suspected ADR (Waller and Harrison-Woolrych, 2017).

2.2.2.3 Taking action

The taking action step of a PV systems is a three-fold approach, which entails (i) considering possible options, (ii) deciding on and selecting the most appropriate option, and (iii) implementing the selected option (Waller and Harrison-Woolrych, 2017). When considering the possible options, both the user and the drug characteristics need to be evaluated and, based on these characteristics, different potential options can be identified. If these recommended options are not sufficient, more comprehensive and often system-level actions, such as regulatory actions or removing the drug from the market, are considered (Lindquist, 2004; Waller and Harrison-Woolrych, 2017). Then, during the decision-making approach, the first step is to compile a document containing all the relevant information, often referred to as a benefit-risk report, which is used by both companies and regulatory bodies to determine the most suitable option to implement. Lastly, during the implementation step, the final option is executed; this may involve market authorization or product information changes, or the removal of the drug from the market entirely (Waller and Harrison-Woolrych, 2017). An important consideration during the implementation step is the urgency of communicating the information regarding the selected option to the different HCP and patients, especially in the case of life-threatening ADRs (Lindquist, 2004; Waller and Harrison-Woolrych, 2017).

2.2.2.4 Communication

Communication within the context of the PV process refers to the sharing of information related to the actions that have to be taken when an ADR is reported or when a drug is being investigated (Waller and Harrison-Woolrych, 2017). According to Waller and Harrison-Woolrych (2017), communication is seen as the most important step of the PV process; and yet, it has proven to be very challenging within the PV context, especially if information needs to be distributed quickly to the involved stakeholders, i.e. PV centres, HCP, pharmaceutical manufacturers and distributors (WHO, 2002c; Waller and Harrison-Woolrych, 2017). When

communicating information regarding drug safety, it is important to ensure that information is accurate, balanced, and transparent, meaning that there is clarity when discussing possible hazards (Waller and Harrison-Woolrych, 2017). Furthermore, the information should also be understandable, ideally communicated in layman's terms, and targeted towards the intended audience group (Waller and Harrison-Woolrych, 2017).

2.3 CHALLENGES ASSOCIATED WITH TRADITIONAL PV SYSTEMS

As stated in Section 2.1, a context-specific PV system needs to not only address the niche factors, but should consider and address the challenges associated with or brought about by the four identified niche factors, i.e., (i) traditional PV systems, (ii) MPP, (iii) HIV, TB and Hepatitis C, and (iv) RLS. The key reasoning supporting this statement is that a context-specific PV system is specifically aimed at addressing the environment of MPP drug provision systems, where these niche factors are integrated and where they require unique considerations, should ideally alleviate the known challenges in a traditional PV system, or at the very least not perpetuate such challenges.

Thus, the challenges associated with traditional PV systems will be identified and investigated in this section. The approach taken to identify these challenges will be discussed first, followed by an overview of these challenges and the challenges landscape related to traditional PV systems that is developed.

2.3.1 Systematic literature review approach

Due to the vast amount of literature available with regard to PV and drug surveillance monitoring, a systematic literature study was conducted to identify the literature most relevant to this study, i.e. literature pertaining specifically to challenges associated with traditional PV systems. The primary search protocol was conducted in the academic database, Scopus⁶, as this is considered the largest and most comprehensive database to consult when using keywords in a search protocol; in addition, the database PubMed⁷ was consulted for serendipitous findings. For this systematic review, three expanded search term sets were developed to ensure that the most relevant articles would be included. The search terms that were used were within the context of challenges associated with PV systems and are shown in Table 2.1.

Table 2.1: List of search terms used for the systematic literature review pertaining to the PV challenges landscape

Database	Search term	Number of documents	Number after 2000
Scopus	("drug monitoring" OR pharmacovigilance) W/5 ⁸ (challenges* ⁹ OR weakness* OR concern* OR issues*)	580	420

⁶ Scopus is the largest database of peer reviewed literature with the format of abstract and citation (<https://www.elsevier.com/solutions/scopus>) (Scopus, 2019)

⁷ PubMed is a database for biomedical literature: <https://www.ncbi.nlm.nih.gov/pubmed/>

⁸ Within the context of Scopus, the term W/5 refers to, within 5 words of each other

⁹ Within the context of Scopus, the * replaces multiple characters in a term, for example behav* finds behave, behaviour, behaviour, behavioural, behaviourism

	("drug monitoring" OR pharmacovigilance) AND challenges*	90	84
	("drug monitoring" OR pharmacovigilance) AND "developing countries" AND challenges*	34	32

A total of 704 articles were identified after the search process, however to ensure that only the most relevant articles were included, certain additional criteria were considered; i.e. documents were limited to documents conducted in English and published between the years 2000 and 2017 were included to insure consistence of the systematic review. After these criteria points were applied, 536 articles were still under consideration and these articles' abstract were screened for relevance with regard to traditional PV systems. Subsequently 73 articles remained which were then reviewed and to ensure that the most relevant articles were included and thus documents that did not consider challenges associated with PV systems were removed. After the completion of this process 33 documents from Scopus and an additional 2 documents from PubMed, were reviewed to identify the challenges found in traditional PV systems. Figure 2.2 provides an overview of the process that was followed during the systematic literature review.

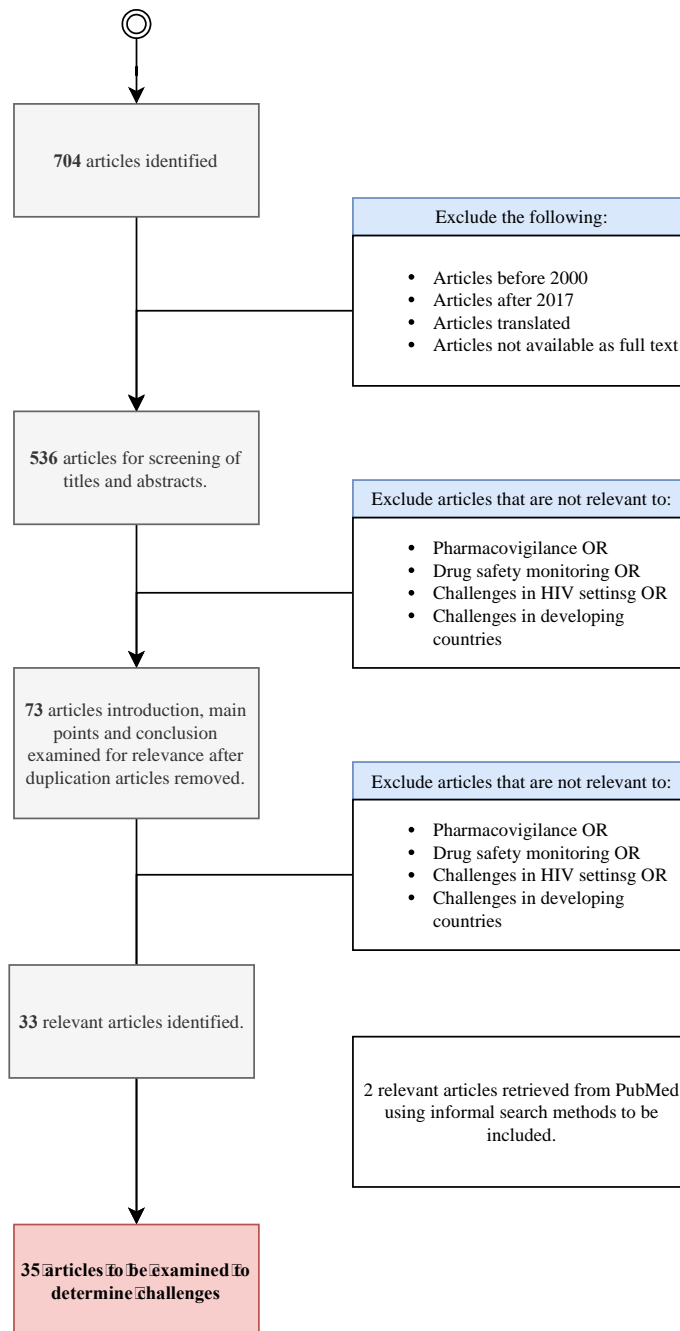


Figure 2.2: Systematic literature review process pertaining to PV challenges

2.3.2 Challenges associated with traditional pharmacovigilance systems

During the systematic review, 20 challenges associated with traditional PV systems were identified. These identified challenges are discussed individually in the following section. The 20 challenges include:

- i. Absence of a PV curriculum;
- ii. Consumers;
- iii. Confidentiality and ethics;
- iv. Detection of ADRs;
- v. Doctors;

- vi. Government and regulatory bodies;
- vii. Inadequate quality of data;
- viii. Incorporation of paediatrics & pregnancy;
- ix. Lack of effective communication channels;
- x. Lack of PV education within the healthcare environment;
- xi. Lack of Knowledge, Attitude and Practices;
- xii. Lack of training;
- xiii. Limited finances;
- xiv. Limited resources;
- xv. Pharmacists;
- xvi. Pharmaceutical companies;
- xvii. Stakeholders involvement;
- xviii. Traditional medicines; and
- xix. Under-reporting of ADR.

2.3.3 Absence of a pharmacovigilance curriculum

Studies have shown that students studying BPharm and PharmD have insufficient knowledge of PV and how to report ADRs, and that there is a need to incorporate these processes into the curriculum of these healthcare studies (Farha *et al.*, 2015). Since pharmacists need to be able to correctly identify ADRs and to report them, as they are often the first line of contact, it is necessary for pharmacy students to be trained in these aspects. Furthermore, incorporating PV subjects into the curriculum of medical students will enhance their KAP, which will advance the healthcare delivery system for the future (Aylin Arici *et al.*, 2015; Abubakar and Haque, 2016). The improvements to the curriculum can be achieved through various applications such as implementing ADR reporting training into undergraduate programs or institute internships and post-graduate training programs (Umair Khan *et al.*, 2015; Abubakar and Haque, 2016).

The PV curriculum can be seen as a subset of PV education, which has also been identified as a challenge, see Section 2.3.13; the literature pertaining to PV education highlights the lack of implementation of a PV curriculum (Lamprecht, Bam and De Kock, 2017).

2.3.4 Absence of a pharmacovigilance culture

A PV system is built on a culture of drug safety, in which the importance of identifying, reporting, and monitoring ADRs is integrated within the healthcare system (Lamprecht, Bam and De Kock, 2017). However, according to the literature, there is a need to address the lack of such a culture in traditional PV systems, which will require the improvement of misconception and general understanding related to PV systems (Vallano *et al.*, 2010; Lamprecht, Bam and De Kock, 2017). It has been stated that integrating education on PV into the healthcare system is necessary to build a culture of PV (Lamprecht, Bam and De Kock, 2017). Similarly, by improving the culture and raising awareness on the importance of PV, it will be possible to overcome other challenges, such as a lack of ADR reporting and stakeholder

responsibility with respect to ADR reporting (Dal Pan, 2014; Matos, Hunsel and Joaquim, 2015).

2.3.5 Consumers

In a PV environment, consumers have to be aware of the importance of ADR reporting; however, studies looking at consumers' KAP with regard to PV show that this has not yet been achieved and that more efforts should be made to engage the public (Thomas and Zachariah, 2017). Furthermore, communication between consumers and HCP are vital, as HCP are responsible for informing consumers on both ADR and PV (Lumpkin, 2000).

2.3.6 Confidentiality and ethics

In the modern-day healthcare landscape, where the use of electronic databases and technology is a growing reality, confidentiality in the healthcare environment poses a bigger challenge than ever before (Tobaiqy *et al.*, 2010; Thomas and Zachariah, 2017). A lack of confidentiality assurance has resulted in consumers being reluctant or fearful of reporting ADRs because they are afraid that their privacy will be compromised if they admit to taking certain medication – specifically in the case of HIV, TB and Hepatitis C (Thomas and Zachariah, 2017). Furthermore healthcare professionals are concerned that reporting ADRs will negatively affect their medical reputation, and subsequently a patients' confidence in the healthcare system, but not reporting ADRs and denying that ADRs occur, on the part of HCP –will also most likely further reduce faith in the healthcare system because it is failing patients (Ronald H.B. Meyboom, 2002; Isah *et al.*, 2012).

2.3.7 Detection of adverse drug reactions

The identification of ADRs together with the detection of the relation between ADRs and drug exposure are a significant challenge faced in PV (Talisuna, Staedke and D'Alessandro, 2006; Isah *et al.*, 2012; Pillay *et al.*, 2017). The lack of ADR detection is often attributed to the lack of KAP and education in PV (Ronald H.B. Meyboom, 2002). According to a study by Abubakar and Haque (2016) this challenge has given rise to new methods of screening reports in order to identify signals, such as automated programs to screen large electronic databases (Abubakar and Haque, 2016).

2.3.8 Doctors

Doctors play a vital role in the PV system, as they are often the first point of contact for the reporting of ADRs and thus should be able to easily identify, manage and report ADRs; it is evident from the literature, however, that one of the main shortcomings of ADR surveillance is poor education of health professionals, including doctors, with regard to PV (Nilseng *et al.*, 2014; Abubakar and Haque, 2016). According to the literature, the curriculum of students in pharmaceutical studies needs to include PV (Dikshit, 2010; Brickel *et al.*, 2017).

2.3.9 Governments and regulatory bodies

Governments have a key role to play in developing and supporting PV systems, and require support through collaborations with safety and regulatory departments (Palaian, 2017; Thomas and Zachariah, 2017). The government plays a vital role with regard to drug registration, drug bans, labelling, usages, and restrictions (Thomas and Zachariah, 2017). However, the KAP, see Section 2.3.14, of PV in the political environment is neglecting, which is negatively

affecting the PV culture (Olsson *et al.*, 2010). The lack of government involvement in PV also negatively affects other areas, such as poor financial support, which has a vital impact in RLS (Lindquist, 2004; Olsson *et al.*, 2010; Miller, Nwokike and Stergachis, 2012; Olivera *et al.*, 2014).

2.3.10 Inadequate quality of data

The impact of incomplete and inadequate quality reports is identified as a pressing concern within PV systems (Lindquist, 2004; Dal Pan, 2014; Kheloufi *et al.*, 2017). In order for a PV system to be effective in all the different stages from retrieval of ADRs to analysis and decision-making, methods should be put in place to ensure that the highest quality of data is received (Kheloufi *et al.*, 2017). Furthermore, it is often also the case that reports are of poor quality, especially in the case of consumer reports, due to a lack of education with regard to PV and ADRs (Dal Pan, 2014). Reports that are of insufficient quality and provide no useful information, or more specifically, information that would be useful to the context of drug safety monitoring, places a further burden on RLS, as resources need to be diverted from important activities to assist with the addressing of these reports (Lester, 2009; Tobaiqy *et al.*, 2010; Isah *et al.*, 2012).

2.3.11 Incorporation of paediatrics and pregnancy

These specific groups of users require specialized needs in a drug monitoring system, which has proven to be challenging in a PV system (Lester, 2009). Studies have shown that there is insufficient information on medicine safety with regard to pregnancies, and thus more attention should be paid to ADR reporting among pregnant women, with specific attention being paid to the fetus (Lester, 2009; Tobaiqy *et al.*, 2010; Isah *et al.*, 2012). Furthermore in the field of paediatrics, more focus should be placed on PV too, as children are classified as a high risk group (Tobaiqy *et al.*, 2010). Consequently, according to Dikshit (2010) it has proven challenging for parents to gain confidence in the healthcare system with regard to paediatric PV, as children are more likely to react negatively to drugs (Dikshit, 2010).

2.3.12 Lack of effective communication channels

Communication between different stakeholders such as healthcare professionals, consumers and other stakeholders is very important in a PV system, which must ensure that accurate information is provided to the different parties (Bahri, 2010; Mehta, Dheda, Steel, M. Blockman, *et al.*, 2014). Thus good platforms for communication should be in place in order for healthcare professionals to communicate both with consumers and the government (Thomas and Zachariah, 2017). However, according to Olsson (2010), it has been found that this is often lacking in PV systems, which leads to poor consumer-provider communication that is further worsened by a lack of resources (Olsson *et al.*, 2010).

2.3.13 Lack of pharmacovigilance education within the healthcare environment

The concept of education in a PV system comprises several different aspects, such as training programs, knowledge of different stakeholders, and culture of ADR reporting (Lumpkin, 2000; Farha *et al.*, 2015; Kheloufi *et al.*, 2017). Furthermore studies have also indicated that students studying medicine, both pharmacists and doctors, have insufficient knowledge on PV and the importance thereof, and that a change in the curriculum of the students is needed in order to encourage and facilitate the identification and reporting of ADRs (Vallano *et al.*, 2010). A lack

of education regarding PV and the PV system also leads to other challenges, such as the identification and reporting of ADRs, communication between different stakeholders and the under-reporting of ADRs (Sevene *et al.*, 2008; Vallano *et al.*, 2010; Abubakar and Haque, 2016). The challenge of improving PV education is a pressing matter, and studies have been conducted on methods on how to address this problem. Both pharmacists and students in the medicine field acknowledge the importance of ADR reporting and agree that training programs, feedback sessions, the implementation of a focal person and continuous PV education should be integrated into the healthcare system, although this still has not been incorporated effectively (Thomas and Zachariah, 2017).

2.3.14 Lack of Knowledge, Attitude and Practice

KAP refers to the knowledge, attitude and practices associated with PV, where knowledge refers to the true understanding of a topic, attitude is how an individual's actions or behaviours are influenced through their beliefs, and practice comprises the actions of an individual, which in this case refers to a HCPs actions in observing, reporting and assessing ADRs (Vallano *et al.*, 2010; Thomas and Zachariah, 2017). From the literature, it is evident that there is a lack of awareness about this system in the PV community, as most healthcare professionals have inadequate knowledge of ADRs and do not always have a positive attitude towards the reporting thereof, largely because reporting ADRs is voluntary (Prabhakar and Edwards, 2010). However, improving KAP may also address other challenges, such as under-reporting, as the participants, whether HCP or consumers, will likely have an improved understanding of the reasons for reporting ADRs and the importance of this process (Olsson *et al.*, 2010; Vallano *et al.*, 2010; Abubakar and Haque, 2016).

2.3.15 Lack of training

The lack of effective training programs for healthcare professions, which includes the lack of PV training in the curriculum of students, is closely related to PV education (Olsson *et al.*, 2010; Abubakar and Haque, 2016). A study by Farha (2015) shows that students comprehend the importance of PV practices and agree that PV training should be integrated into the curriculum, although this is found to still be challenging (Farha *et al.*, 2015). Moreover, students should be trained how to effectively recognize, avoid and report ADRs, as this will reduce under-reporting (Isah *et al.*, 2012; Abubakar and Haque, 2016). The implementation of training in the curriculum will also alleviate the challenge of KAP (Olsson *et al.*, 2010; Isah *et al.*, 2012; Skalli and Soulaymani Bencheikh, 2015).

2.3.16 Limited finances

Limited finances in the field of PV has been shown to pose a major challenge, especially in developing countries, where basic PV needs are often not being met (Simoooya, 2005; Olsson *et al.*, 2010). In a study conducted by Skalli and Soulaymani Bencheikh (2015) it was found that poor funding to PV in the healthcare system can be attributed to stakeholders not comprehending the importance of a PV system and thus not allocating resources to it (Skalli and Soulaymani Bencheikh, 2015). Such a lack of finances does not only directly affect the PV programs of a country but also the PV training programs (Talisuna, Staedke and D'Alessandro, 2006; Dal Pan, 2014).

2.3.17 Limited resources

For a PV system to work effectively, resources, such as people, time and money, are required, but in the traditional PV system, little attention has been paid to such resources (Talisuna, Staedke and D'Alessandro, 2006; Mudzviti *et al.*, 2012; Dal Pan, 2014). A lack of resources further makes it difficult to identify and ascertain the seriousness of ADRs, as the available resources often lack PV education (Mudzviti *et al.*, 2012).

2.3.18 Pharmacists

As pharmacist are often the first line of contact for reporting ADRs, they have a vital role to play in PV; however, there are issues that prevent them from assisting in this process. In most developing countries, there is a lack of qualified personnel, which results in under-reporting and low quality standards of reporting (Dikshit, 2010; Nilseng *et al.*, 2014; Olivera *et al.*, 2014). Furthermore, the lack of a culture of drug safety reporting has created an environment where HCP, such as pharmacists are not aware of the importance of PV and thus often do not receive the necessary education on how to identify and report ADRs (Dikshit, 2010; Olivera *et al.*, 2014).

2.3.19 Pharmaceutical companies

A challenge that often arises when considering PV is the extent of involvement from the private sector and pharmaceutical companies (Jeetu and Anusha, 2010; Isah *et al.*, 2012; Dal Pan, 2014). Pharmaceutical companies are under pressure to ensure that the quality of their products is up to standard with regulations, and thus have been encouraged to improve collaboration with the PV system (Jeetu and Anusha, 2010). However, it has been found that generic pharmaceutical companies do not always recognize or accept their responsibility in continuous drug safety monitoring (Baroutsou, 2009; Dal Pan, 2014).

2.3.20 Stakeholder involvement

PV is a collaborative endeavour that involves multiple stakeholders from different fields. The involvement of the HCP raises challenges that need to be considered (Dikshit, 2010; Dal Pan, 2014). Furthermore, the involvement and role of the government as stakeholder also needs to be considered, as the government has a key role to play with regard to ensuring that the PV programs are sustainable and achievable (Palaian, 2017; Thomas and Zachariah, 2017). The extent and nature of the involvement of the private sector, in the form of pharmaceutical companies, also raises challenges for PV systems that need to be overcome (Skalli and Soulaymani Bencheikh, 2015).

2.3.21 Traditional medicine

With the growing use of herbal and/or traditional medicines, especially in developing countries (Isah *et al.*, 2012; Skalli and Soulaymani Bencheikh, 2015), challenges regarding PV and the need for monitoring of these products are increasing, and call for the adaptation of PV systems (Skalli and Soulaymani Bencheikh, 2015). Studies have shown that, as with all medicines, traditional medicine too may cause ADRs to appear, often due to incorrect dosages, herb-drug interactions, contamination and mistaken use (Skalli and Soulaymani Bencheikh, 2015). To improve traditional medicine drug monitoring, educational campaigns and training programs should be incorporated into PV systems (Olivera *et al.*, 2014; Abubakar and Haque, 2016).

2.3.22 Under-reporting of adverse drug reactions

Under-reporting of ADRs by HCP and consumers is one of the most challenging issues in PV (Tobaiqy *et al.*, 2010; Isah *et al.*, 2012; Matos, Hunsel and Joaquim, 2015; Abubakar and Haque, 2016). According to a study done by Matos (2015), there are several factors regarding knowledge and attitude that affect under-reporting, such as complacency, diffidence, ignorance, insecurity and indifference (Isah *et al.*, 2012). Other challenges include a lack of knowledge on reporting requirements, an inability to identify ADRs, and insufficient ADR reporting forms and methods (Isah *et al.*, 2012; Dal Pan, 2014). Although it is important to educate health professionals on the importance of ADR reporting, it is just as important to ensure that patients comprehend that consumer reporting is also a vital part of PV (Vallano *et al.*, 2010; Lamprecht, Bam and De Kock, 2017).

2.4 OVERVIEW OF CHALLENGES LANDSCAPE RELATED TO TRADITIONAL PV SYSTEMS

From the identification, and contextualisation of the challenges related to traditional PV systems, as discussed in Section 2.3, it is deduced that certain challenges are inter-related and furthermore impact the PV process at (possible) different stages. Thus, in order to gain a more holistic view of the challenges identified with regard to traditional PV systems, a challenges landscape is developed, showing the different impacts of and relationships between the challenges, if any exists, as well as where these challenges affect the different stages of a PV system. This challenges landscape pertaining to traditional PV systems will form part of the larger challenges landscape by considering the entirety of the MPP drug provision system, which is developed during the later phase of this dissertation.

In this section the landscape development methodology is discussed after which a relationship diagram pertaining to the identified challenges will be developed to assist with synthesising these challenges to create a landscape.

2.4.1 Challenges landscape development methodology

During the process of developing the challenges landscape in the context of traditional PV systems, a relationship diagram is firstly developed in order to determine if any relationships exist between the different identified challenges. These relationships are deduced from the insights gained in the discussion of the challenges as discussed in Section 2.3. Furthermore, based on the discussion of the different challenges it was deduced that these challenges affect the PV process, as discussed in Section 2.2.2 at different stages, and thus these impacts were also considered during the development of the challenges landscape.

The relationship diagram is used to gain insights on the possible relations between the challenges and deductions are made with respect to challenges that can be grouped together based on overarching characteristics, i.e. shared attributes. Building on these insights with respect to the grouped challenges, a challenges landscape pertaining to traditional PV systems is created. In the following sub-sections, the relationship diagram and challenges landscape are discussed in more detail.

2.4.2 Relationship diagram

Once the challenges related to traditional PV had been identified and discussed the interactions and relationships between the identified challenges could be investigated. These relationships refer to, but are not limited to, the impact that these challenges have on one another, i.e. with one challenge contributing to, aggravating, or alleviating another challenge. Furthermore, a relationship between two challenges could also indicate a resemblance between the relevant characteristics and thus lead to the possible grouping of challenges together. The relationship diagram for the PV challenges landscape is provided in Figure 2.3 below.

	Stakeholders	Education	Under-reporting	KAP	Quality of data	Training	Consumers	Pharmaceutical companies	Detection of ADR	Limited resources	Doctors	Traditional medicine	Communication	Lack of finances	Government	Pharmacists	Confidentiality/ ethical	Paediatric/ pregnancy	PV culture	Curriculum
Stakeholders		X					X	X							X	X			X	
Education			X						X										X	X
Under-reporting				X	X	X														X
KAP						X	X		X		X				X	X				
Quality of data							X			X	X			X						
Training												X								X
Consumers													X				X			
Pharmaceutical companies											X		X			X	X			
Detection of ADR										X								X		
Limited resources																				
Doctors													X				X			
Traditional medicine																				
Communication																				
Lack of finances																				
Government																				
Pharmacists																			X	
Confidentiality/ ethical																		X		
Paediatric/ pregnancy																				
PV Culture																				
Curriculum																				

Figure 2.3: Relationship diagram for PV challenges landscape

2.4.3 Challenges landscape

Once the different relationships were derived, the challenges were grouped together based on overarching characteristics, i.e. shared attributes; in this way, three overarching groups of challenges were identified, namely: (i) education, (ii) stakeholders, and (iii) reporting inefficiencies. The challenges associated with education were attributed to a lack of education relating to PV within the healthcare system, the challenges related to stakeholders refer to the different stakeholders' involvement within the PV system and their specific roles, and the reporting inefficiencies were seen as challenges that are directly caused by inadequacies in the reporting process. Furthermore, from the discussion of the challenges and the developed relationship diagram, it was found that the PV culture posed an overarching challenge that directly affected education, stakeholders and inadequacies in the PV process, thus indirectly affecting those challenges within these groups (see Figure 2.4).

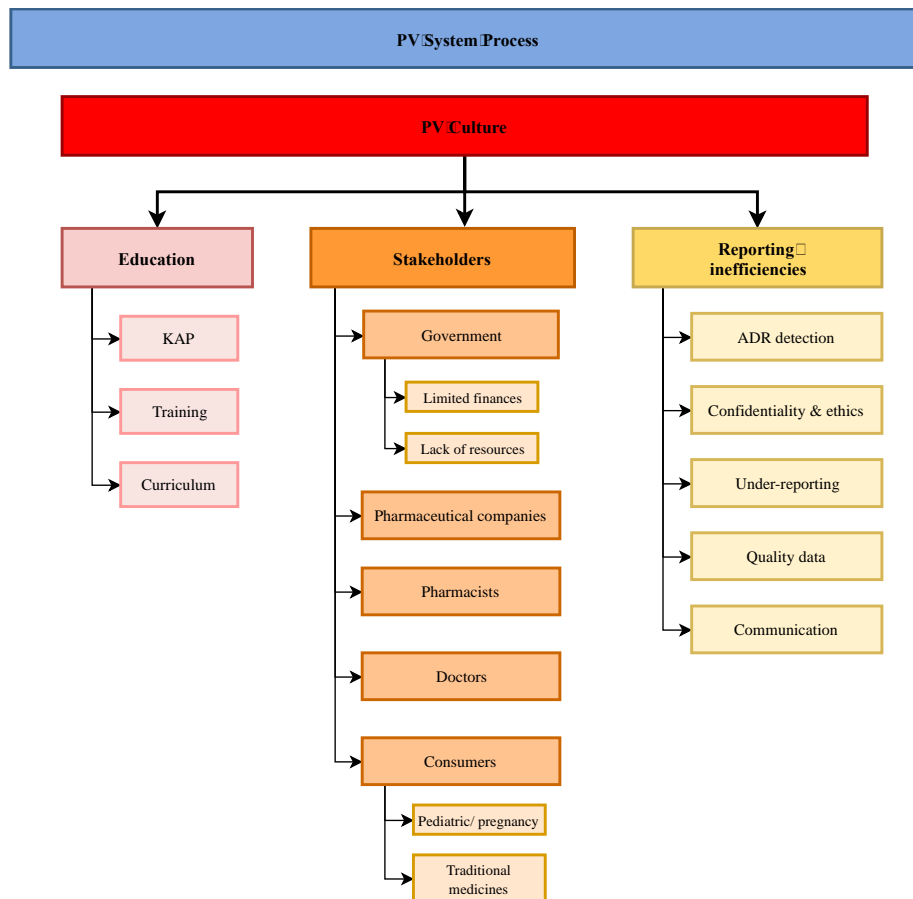


Figure 2.4: PV challenges within the context of PV culture

The challenges landscape related to traditional PV systems was developed based on the groupings of the challenges within the context of PV culture within the context of the different PV process as discussed above. The challenges landscape related to traditional PV systems is illustrated in Figure 2.5 while the typology and the groupings are summarised in Table 2.2. In Table 2.2, the code number, as indicated in Figure 2.5, along with the challenges group, the different challenges, are provided. Furthermore, the discussion of the typology, in terms of Table 2.2, also clarifies how and if the specific challenges group affects the other identified challenges.

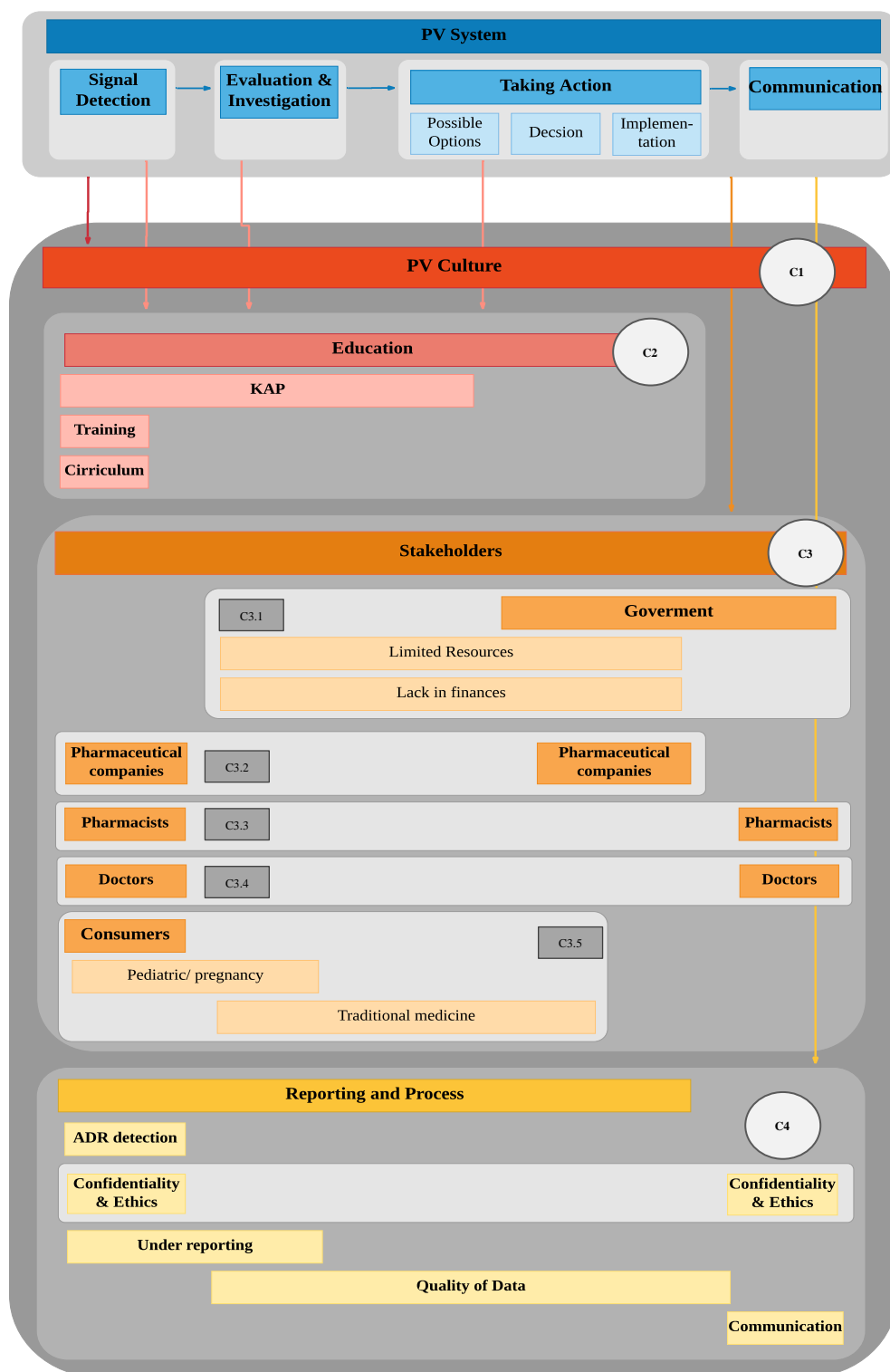


Figure 2.5: Typology of challenges landscape pertaining to traditional PV systems

Table 2.2: PV challenges landscape discussion

Code	Challenges group	Grouping	Explanation		
C1	PV culture	PV Culture, Stakeholders, Education, Reporting & Process.	As previously mentioned from the literature review, it could be deduced that the over-arching challenge with regard to PV was the culture associated with PV and the PV process. It was determined that this culture affects all the other identified challenges, either directly or indirectly. The effects of the PV culture directly implicate the stakeholders, education and the reporting system. For example, creating a culture focused on the importance of PV will positively influence stakeholder involvement, leading to increased reporting of ADRs and improvement in the education of PV throughout the entire PV system (Vallano <i>et al.</i> , 2010)		
C2	Education	Education, KAP, Training, Curriculum	Education is one of the main challenges that affects different stages of the PV system; there are many different challenges that are caused by a lack of PV education, such as detection of ADRs, under-reporting and inadequate quality of reports (Prabhakar and Edwards, 2010). PV education is mainly related to KAP, training programs and student healthcare curriculums, which are often found to be lacking, thus causing further challenges. For example, a low KAP often leads to under-reporting of ADRs, since most stakeholders do not comprehend the importance of PV (Isah <i>et al.</i> , 2012; Abubakar and Haque, 2016). This issue of KAP can be addressed by implementing training programs and improving the curriculum of students in healthcare (Baroutsou, 2009; Dal Pan, 2014). Without effective training programs and relevant subjects within study fields, education with regard to PV would be ineffective, thus leading to a lack of detection of ADRs, a lack of stakeholder involvement, and under-reporting.		
C3	Stakeholders	Stakeholders, Government, Pharmaceutical companies, Pharmacists, Doctors, Consumers	As mentioned, PV is a collaborative undertaking that actively involves all stakeholders, such as the government and the pharmaceutical and health industry professionals, but a lack of involvement by these stakeholders has been found, leading to further implications and challenges that affect the PV system negatively (Sabblah <i>et al.</i> , 2015; Thomas and Zachariah, 2017)		
			<i>Code</i>	<i>Grouping</i>	<i>Explanation</i>
			C3.1	Government, Limited resources, Lack of finances	As mentioned, the government has a vital role to play in the PV process with regard to decision making and implementation of the actions taken, and then communicating these decisions to those involved. Furthermore, it has been found that the lack of government involvement is associated with a lack of finances and low resources being allocated to PV, which again relates back to the lack of KAP in respect of PV within the political environment (Mudzviti <i>et al.</i> , 2012; Skalli and Soulaymani Bencheikh, 2015). Such a lack of resources creates further challenges, such as effectively identifying ADRs, whereas the lack of finances also implicates PV education, such as training programs (Waller and Harrison-Woolrych, 2017).

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Code	Challenges group	Grouping	Explanation		
C3	Stakeholders	Stakeholders, Government, Pharmaceutical companies, Pharmacists, Doctors, Consumers	<i>Code</i>	<i>Grouping</i>	<i>Explanation</i>
			C3.2	Pharmaceutical companies	The involvement of pharmaceutical companies is often a challenge in itself, as there is commonly a conflict of interest between healthcare delivery systems and the pharmaceutical industry, which affects PV. Furthermore, pharmaceutical companies are mostly involved during the decision making and implementation step of the PV process, as they are directly involved with the manufacturing of the drugs that are being investigated (Mudzviti <i>et al.</i> , 2012).
			C3.3	Pharmacists	As pharmacists are often the first line of contact, they are mostly involved during the signal detection step, with regard to identifying and reporting ADRs (Mudzviti <i>et al.</i> , 2012; Nilseng <i>et al.</i> , 2014). However, due to the lack of a PV culture and education in relation to PV, pharmacists are often not able to correctly identify ADRs, leading to under-reporting and low-quality reports (Farha <i>et al.</i> , 2015). Improvements in the curriculum will positively affect pharmacists' abilities in this regard (Abubakar and Haque, 2016; Thomas and Zachariah, 2017).
			C3.4	Doctors	Doctors are mostly involved during the detection and reporting of ADRs; however, this has proven to be challenging, and under-reporting has been associated with doctors' lack of involvement. This is often due to the poor PV education in the healthcare system, and the ethical issues that doctors have with regard to reporting and their busy schedules (Nilseng <i>et al.</i> , 2014; Abubakar and Haque, 2016). However, improvements in the curriculum could overcome these challenges (Skalli and Soulaymani Bencheikh, 2015).
			C3.5	Consumers, Paediatric/ pregnancy, Traditional medicines	In the PV process, consumers are mostly involved with the reporting of ADRs and symptoms to either doctors or pharmacists; however, due to a lack of KAP, consumers often do not understand the importance of PV. Furthermore, certain specialized groups, namely pregnant women and users of traditional medicine create further challenges. The main challenges in these cases are the lack of education with regard to PV, which is often associated with an absence of PV in training program, curriculum or public awareness (Thomas and Zachariah, 2017). A lack of paediatric monitoring has also often been associated with ethical and confidentiality issues that parents have with the reporting process. Moreover, a lack of communication between consumers and HCP is one of the leading challenges with PV and ADR reporting (Isah <i>et al.</i> , 2012).
C4	Process inefficiencies	Reporting & Process, ADR detection, Confidentiality & ethics, under reporting, quality of data	In the process of reporting, it has been found that many challenges can be inter-related, such as detection of ADRs, ethics, quality of data and under-reporting, which has been found to be one of the biggest challenges faced in PV. Under-reporting further relates to challenges, such as detection of ADRs and a lack of knowledge with regard to reporting requirements (Dal Pan, 2014; Thomas and Zachariah, 2017). The inadequate quality of the data is often attributed to the lack of resources, whereas ethical issues are related to the involvement of certain stakeholders, such as doctors (Isah <i>et al.</i> , 2012; Dal Pan, 2014; Kheloufi <i>et al.</i> , 2017). However, most of these challenges can be attributed to the lack of PV related education within the healthcare system (Modell, 2003).		

2.5 CHAPTER 2 CONCLUSION

In this chapter, the input identification phase was executed, with the aim of contextualising the first niche factor, viz., traditional PV systems, which needs to be taken into account when developing a decision support tool that facilitates the development of context-specific PV systems within the environment of MPP drug provision systems.

In addition to the contextualisation of traditional PV systems, challenges associated with this factor were also identified and investigated, and a challenges landscape related to traditional PV systems was developed in order to gain a systems perspective understanding of these challenges and the impact that they have on the PV process.

In the following chapter, the input identification process will be continued, but the focus will be placed on the contextualisation of the other identified niche factors, (i) MPP, (ii) HIV, TB and Hepatitis C, and (iii) RLS. Furthermore, challenges associated with these factors will also be investigated, as was the case in this chapter, and the developed PV challenges landscape will be amended to include the additional challenges. In this way, a challenges landscape for all the niche factors associated with the environment of MPP drug provision systems will be developed.

Chapter 3: Niche factor contextualisation: Medicine Patent Pool, HIV, TB and Hepatitis C, and resource limited settings

In this chapter, the input identification phase of the systems engineering approach will be continued by focusing on the environmental context of MPP drug provision systems. The same approach that was used in Chapter 2, viz. to contextualise the first niche factor, namely, (i) traditional PV systems, will be followed in this chapter, but with regard to the three other identified niche factors, (ii) the MPP, (iii) HIV, TB and Hepatitis C, and (iv) RLS.

When considering the aim of this research inquiry of developing a decision support tool that facilitates the development of context-specific PV in particular for the environment of MPP drug provision systems, it is necessary to consider the factors that could influence such a proposed system. However, as stated in Section 2.1 given the context of this dissertation, an in-depth input identification process is not required; it has already been established that the environment under consideration, i.e., MPP drug provision systems, comprises four niche factors as stated above. Furthermore, to ensure that the proposed context-specific PV system adequately addresses all of these factors, it is necessary to identify any challenges associated with them.

In Chapter 2, the first niche factor, traditional PV systems, and challenges associated with this factor, was investigated and discussed in order to gain a systems level understanding of PV. In this chapter the other three niche factors will be contextualised, after which a systematic literature review will be conducted to identify any challenges related to these factors within the context of PV. This will lead to the development of a challenges landscape. Moreover, in order to gain a systems level perspective of all the challenges related to the context of this dissertation, the challenges landscape developed in Chapter 2 and in the current chapter will be synthesised to form a single challenges landscape. This phase of the research is illustrated in Figure 3.1.

It should be noted that a substantial portion of this chapter has been published as a journal article in the SAJIE, the publication is shown in Appendix A.

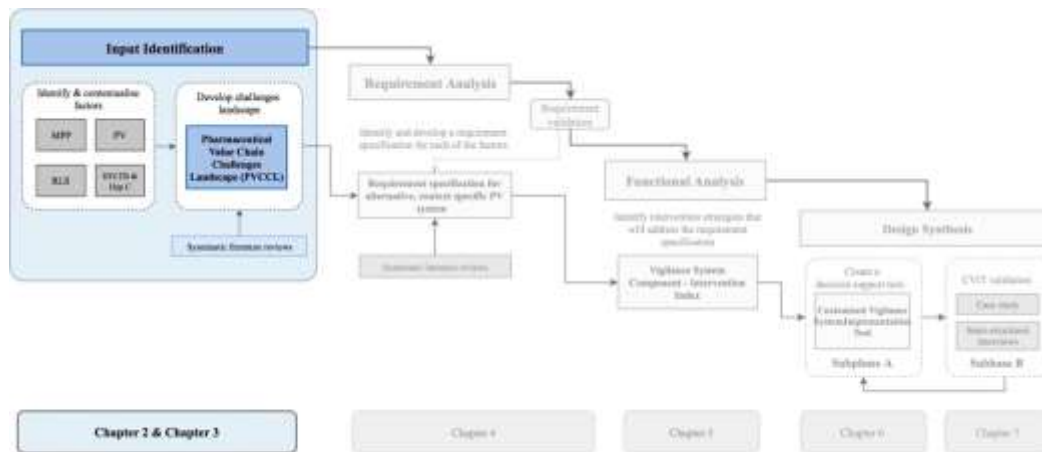


Figure 3.1: Systems engineering approach: Input identification related to MPP, HIV, TB and Hepatitis C, and RLS

3.1 NICHE FACTOR CONTEXTUALISATION

When considering a context-specific PV system within the context of MPP, there are four niche factors that need to be considered, namely: (i) traditional PV systems (which was discussed in Chapter 2), (ii) the MPP, (iii) the disease burden addressed by the MPP (HIV, TB and Hepatitis C), and (iv) RLS. This section looks at the context of the latter three niche factors within PV systems.

3.1.1 The Medicine Patent Pool

In developing countries, it was found that patients were often not receiving treatment for certain disease, such as HIV and TB, due to the high costs of the patent system, which gave some companies a monopoly over a certain drug (Modell, 2003). Thus, in 2010, the MPP was established by UNITAID to increase access to specific communicable disease treatments, namely HIV, Hepatitis C and TB, in low- and middle-income countries by sharing technologies and patents (Modell, 2003). A patent pool is defined as a collaboration between patent holders and other third parties, where licences are offered for usage in exchange for a price or royalties. The implementation of a medicines patent pool allows drugs to be produced and distributed to a broader population, at a faster rate and at a more affordable price (Modell, 2003; UNITAID, 2010; Medicine Patent Pool, 2011; Perry, 2012). The WHO assists the MPP by prioritising the required medicines, while patent holders voluntarily agree to license their medicines to the MPP, who in turn agree to licence manufacturing rights to generic pharmaceutical companies.

The implementation of the MPP has numerous advantages, such as facilitating competition, increasing low-cost manufacturing and encouraging research and development (R&D) (Perry, 2012). Moreover, it encourages competition, as multiple drug manufacturing companies can access the same patents. As competition increases, it may decrease drug prices, leading to more affordable drugs being available (Modell, 2003). Through the MPP, numerous pharmaceutical manufacturing companies are also able to approach the patent pool to negotiate licensing agreements to create generic versions of these drugs (Modell, 2003; UNITAID, 2010; Medicine Patent Pool, 2011; Perry, 2012). The MPP encourages R&D as the patents for

the drugs are easily accessible and can thus be used to develop new fixed-dosage combinations in order to create appropriate formulations to meet the specific needs of the patients, as the drugs are often not adapted for usage in developing countries (Burrone, 2016).

However, there are also certain challenges, such as inadequate generic pharmaceutical manufacturing and distribution systems, a lack of R&D, sub-standard medicines, and other regulatory challenges of providing access to medicine through the MPP (T’Hoen *et al.*, 2011; Taylor *et al.*, 2011). The challenges associated with the MPP within the context of PV are discussed in detail in Section 3.2 below. The patents, which are accessible through the MPP, are made available at no cost, to any generic pharmaceutical manufacturing company in low- and middle-income countries that wishes to make use of it (T’Hoen *et al.*, 2011; Taylor *et al.*, 2011). Although such generic pharmaceutical manufacturers do need to meet certain quality standards, it is often challenging to monitor and enforce these standards of quality. This is why effective drug safety monitoring systems must be considered and implemented. From research, it is evident that, that the drug manufacturing and distribution systems, which are made possible through the MPP, result in numerous challenges, such as counterfeit, or substandard drugs, which reaffirms the need for effective drug safety monitoring systems (Medicines Patent Pool, 2010b, 2010a).

3.1.2 Medicine Patent Pool related disease burden: HIV, TB and Hepatitis C

The MPP makes available patents for certain drugs to increase access to and facilitate the development of treatments related to HIV, TB and Hepatitis C, as these communicable diseases are highly prevalent in environments targeted by the MPP, i.e. developing countries, and as they are often the biggest contributor to the high burden of diseases (WHO, 2019d).

The three communicable diseases addressed by the MPP, are discussed in more detail in the following subsections.

3.1.2.1 HIV/AIDS

HIV is an immunodeficiency virus that weakens a person’s immune system and increases susceptibility to other infections and diseases. The most advanced stage of HIV is AIDS; it can take up to 15 years to develop this, depending on the specific individual. The virus is transmitted through bodily fluids (WHO, 2019d).

HIV/AIDS is a global public health issue, which has caused more than 32 million deaths to date. In 2018, 770 000 had died from AIDS whilst approximately 37.9 million people are still living with the disease. Furthermore, according to the WHO, the African region accounted for almost two thirds of the 1.7 million newly infected HIV patients of 2018 (WHO, 2019d). Although access to treatment for HIV infected patients has been improving, 48% of these patients in low-and-middle income countries do not have access to antiretroviral treatment (ART) (Medicines Patent Pool, 2010a).

These statistics indicate that HIV is still seen as a prevailing diseases in developing countries, which reaffirms the need for innovative drug manufacturing platforms such as the MPP. ART is used to treat HIV-infected patients, by supressing the replication of the HIV virus, which thus prevents the weakening of the infected patient’s immune system. The MPP attempts to address the prevalence of HIV in developing countries by allowing generic pharmaceutical

manufacturing companies access to patents for the following ARTs (Medicines Patent Pool, 2010a; Angamo *et al.*, 2016; Tetteh *et al.*, 2016)

- i. Atazanavir;
- ii. Bictegravir;
- iii. Cobicistat;
- iv. Dolutegravir;
- v. Elvitegravir;
- vi. Emtricitabine;
- vii. Lopinavir, Ritonavir;
- viii. Patents related to Darunavir;
- ix. Solid drug nanoparticle technology;
- x. Tenofovir Alafenamide;
- xi. Tenofovir Disoproxil Fumarate; and
- xii. Valganciclovir.

Apart from these ARTs, the MPP also allows access to the following four paediatric related ARTs:

- i. Abacavir;
- ii. Dolutegravir (paediatric specific);
- iii. Lopinavir, Ritonavir (paediatric specific); and
- iv. Raltegravir.

Within the context of drug safety monitoring, there are HIV related challenges, such as the high occurrence of ADRs, that have to be addressed and taken into account when considering a context-specific PV system (WHO, 2018c). Section 3.2 provides a more detailed explanation of these challenges.

3.1.2.2 TB

Tuberculosis is an airborne bacterial disease that affects the lungs and can thus rapidly be spread if infected patients are not treated timeously and effectively (WHO, 2018c). An infected patient could also have latent TB, which is referred to when the patient does not exhibit symptoms of the disease and cannot transmit it; however, in the case of activated TB, an infected patient could infect up to 10 – 15 people through close contact in the time span of one year (WHO, 2018c). Furthermore in the case that a patient has a compromised immune systems, i.e. such as the case for HIV patients, said patient is at a higher risk of falling ill with TB and developing co-infections, which are often more challenging to address and treat (Medicines Patent Pool, 2019).

Like HIV, TB is prevalent in developing countries. Thus, the MPP seeks to improve access to treatments for this disease by allowing access to the drug, Sutezoid, which is licensed by

Pfizer¹⁰. Sutezoid is an investigational TB drug that, when accessed through the MPP, can be studied further to improve the potential impact with respect to new TB regimes (Chen *et al.*, 2015; Winston and Underwood, 2015; Masuka *et al.*, 2018).

As is the case with HIV, effective PV system are required which consider the manufacturing of TB drug treatments, and thus challenges associated with this disease should also be taken into account when addressing a context-specific PV system (WHO, 2019c).

3.1.2.3 Hepatitis C

Hepatitis C is a blood-borne viral disease that ranges in severity from mild disease to a fatal, lifelong disease which can lead to severe complications, such as liver cancer (WHO, 2019c). The Hepatitis virus is carried through the blood and is most commonly transmitted through the sharing of injectable materials, transfusion of unscreened blood, or sexual practices that lead to blood exposure. However, it can also be transmitted from mother to child during pregnancy or through sexual intercourse. Research done by the WHO indicates that Hepatitis C mostly affects the Eastern Mediterranean region (i.e. Afghanistan, Egypt, Iraq, Qatar, and Saudi Arabia to name a few), an area in which drug manufacturers also have access to the MPP (WHO, 2019c). In 2016, 399 000 people died from Hepatitis C globally, although the use of antiretroviral medication is claimed to cure more than 95% of the infected patients. However, access to diagnosis and treatment is very low, especially in developing countries (WHO, 2019c). In 2017, of the 71 million Hepatitis C patients, only 19% knew their diagnosis and of that group only 38% were being treated most likely due to a lack of access to treatment (WHO, 2019c). Clearly, such challenges need to be addressed in order to ensure that the Sustainable Development Agenda¹¹ 2030 target for Hepatitis C treatment is met, which is aimed at reducing viral hepatitis infections with 90% and deaths by 65% by 2030 (Medicines Patent Pool, 2010a).

Through the MPP, access to the following three Hepatitis C related drugs is made available to generic pharmaceutical manufacturing companies (Fitzgibbon and Wallis, 2014; Geiling *et al.*, 2014). These three drugs are:

- i. Daclatasvir;
- ii. Glecaprevir/Pibrentasvir; and
- iii. Ravidasvir.

As is the case with the previously discussed diseases, HIV and TB, Hepatitis C must also be taken into account when developing a decision support tool that facilitates the development of context-specific PV systems for the context of the MPP.

3.1.3 Resource limited settings

The MPP is implemented in developing countries that are often faced with the challenge of having limited resources available, which may lead to additional challenges within the context of PV systems. RLS, also referred to as resource-poor or resource-constrained settings, are

¹⁰ One of the largest US pharmaceutical companies.

¹¹ This agenda was adopted in 2015 by all United Nations Member States as a plan for peace and prosperity related to the planet considering the impact for the future. The agenda has 17 Sustainable Development Goals.

defined as environments where the capability to provide care to life-treating illnesses is limited to the provision of basic resources, i.e. financial, academic, and human (Sevene *et al.*, 2008; Geiling *et al.*, 2014). These RLS are often characterised by having limited access to medical equipment and supplies, inadequate infrastructures with limited access to maintenance, a limited number of trained HCP to meet the need of the population, or insufficient capacity to deal with a high disease burden (Kinfu, Poz and Evans, 2009).

A study of healthcare workers in sub-Saharan Africa indicated that the number of healthcare workers available was not sufficient for meeting the patients' needs (Mohr, 2006). This is confirmed by studies done by the WHO, which have further found an uneven distribution of healthcare workers globally, with countries that have the highest need of patient care also having the lowest number of HCP (Mohr, 2006). A study conducted by the WHO in (2006) states that, although the African region has more than 24% of the global burden of diseases, this region only has access to 3% of the world's HCP (WHO, 2019b).

Recent statistics from the WHO's Global Health Observatory data repository¹² showed that, in 2017, there were only 9.1 medical doctors per 10 000 population in South Africa, in comparison to the United Kingdom's 28 per 10 000. Other developing countries also had very low doctor-to-patient ratios, such as Angola (2.1/10 000), Ghana (1.8/10 000), India (7.6/10 000) (WHO, 2019a).

Furthermore, this uneven distribution of human resources is not only applicable to medical doctors, but also extends to all types of HCP, pharmaceutical personnel and nurses. The *Global Health Observatory data repository* shows that, in 2017, there were only 1.52 pharmacists per 10 000 population in South Africa, which was more than 6 times lower than the United Kingdom, which had 8.8 per 10 000 (Kinfu, Poz and Evans, 2009). Research also indicates that the pre-service training of healthcare workers in developing countries is insufficient for meeting current and future health needs (Kotagal *et al.*, 2009; Fonjuno *et al.*, 2012).

Moreover, resource limitations do not only refer to human resources, as mentioned. The literature pertaining to healthcare systems in low- and middle-income countries also argues that it extends to a lack of finances, which subsequently results in a lack of medical supplies, equipment, and infrastructure, including poor access to healthcare (Kotagal *et al.*, 2009; Fonjuno *et al.*, 2012). Limited finances also lead to unreliable quality processes, delays in treatment, and a lack of information to support clinical decisions (Urmila, Brown and Yajnik, 2011). In Section 3.2, more detail will be provided on the challenges associated with RLS.

Furthermore, RLS also considers the lack of academic research with respect to specific niche aspects. In RLS environments, academic research is often prioritised to consider the highest healthcare related needs within the environment – which is often focused on the treatments of the most prevalent illnesses (WHO and The Global Fund, 2010).

The WHO states that, for a PV system to function effectively, trained staff and a PV system (infrastructure) needs to exist (Taylor *et al.*, 2011; Burrone, 2016); in RLS, however, this is

¹² <https://www.who.int/gho/en/>

challenging. Thus, when considering the development of a new PV system within the environment of MPP drug provision systems, it is evident that RLS will need to be addressed.

3.2 CHALLENGES ASSOCIATED WITH THE MEDICINE PATENT POOL, HIV, TB, AND HEPATITIS C, AND RESOURCE LIMITED SETTINGS

As mentioned earlier, the challenges that arise in the manufacturing and distribution of those drugs of which patents are made available through the MPP, can be attributed to inadequate drug manufacturing and distribution systems (Naicker *et al.*, 2009). These challenges affect patient safety and thus need to be addressed to ensure that the necessary monitoring systems are in place. The low- and middle income countries that incorporate the MPP also often have limited resources, which poses further challenges (WHO, 2002a).

The aim of this section is to identify the challenges relating to drug manufacturing and distribution systems in RLS, especially with regard to HIV, TB and Hepatitis C. These challenges are identified through a systematic literature review in order to develop a challenges landscape (similar to the PV challenges landscape developed in Chapter 2), which will create a systems level perspective with a context-specific understanding of the relevant challenges. Thereafter, this challenges landscape will be integrated with the challenges landscape developed in Chapter 2 pertaining to traditional PV systems, to develop an overarching challenges landscape within the context of MPP drug provision systems.

In the following section, the approach of the systematic literature review, as well as its findings and results, will be presented, together with a discussion of the identified challenges.

3.2.1 Systematic literature review approach

As was the case with the systematic literature review presented in Section 2.3.1, the academic database Scopus was consulted to identify literature pertaining to PV systems and drug safety monitoring, in order to subsequently identify the challenges associated with (i) the MPP, (ii) HIV, TB and Hepatitis C, and (iii) RLS within the context of PV. PubMed was also used for informal search methods and serendipitous findings.

A total of 2307 relevant articles were found via Scopus, using specific key words and phrases (shown in Table 3.1). In order to find the most relevant documents, inclusion / exclusion criteria were included in the search protocol. Only documents from 2010 – 2017 were included, as the MPP was only introduced in 2010. Furthermore, documents that were not primarily published in English, and thus translated, and any duplicate documents were excluded. Applying this criterion 1302 relevant articles were identified of which the abstracts of these documents were reviews with context to (i) drug manufacturing or (ii) distribution systems or (iii) RLS or (iv) HIV, TB or Hepatitis C, and irrelevant articles were removed. The remaining articles, a total of 107, were then reviewed with respect to challenges within the context of (i) drug manufacturing or (ii) distribution systems or (iii) RLS or (iv) HIV, TB or Hepatitis C, of which only 57 relevant articles were found. An additional 7 articles were found using serendipitous search methods in PubMed. A total of 64 articles were then reviewed in order to identify the relevant challenges. This process is depicted in Figure 3.2.

Table 3.1: List of search terms used for MPP, RLS and specific diseases in the systematic literature review

Database	Search terms	Number of articles	Number after 2010
Scopus	“Drug Manufacturing”	480	257
	“Drug Manufacturing” AND Challenges	45	31
	“Drug Manufacturing” AND HIV	4	1
	“Drug Manufacturing” AND “Developing Countries”	16	8
	“Drug Manufacturing” AND Challenges AND “Developing Countries”	3	1
	“Drug Manufacturing” AND Quality	188	102
	“Drug Distributions” AND Challenges AND HIV	232	147
	“Drug Distributions” AND Challenges AND “Developing Countries”	14	7
	“Drug Resistance” AND HIV AND “Developing Countries”	352	189
	“Counterfeit drugs” AND “Developing Countries”	126	84
	“Resource Limited Settings” AND Challenges AND HIV	337	257
	“Resource Limited Settings” AND Challenges AND “Developing countries”	144	123
	“Patient safety” AND HIV AND “Developing Countries”	24	17
	“Drug Packaging” AND Challenges AND HIV	10	5
	“Drug Packaging” AND Challenges AND “Developing Countries”	9	8
	“Adverse Drug Reactions” AND “Drug Manufacturing”	58	29
	“Adverse Drug Reactions” AND HIV AND “Developing countries”	84	64
	“Drug Manufacturing*” AND Tuberculosis	5	5
	“Drug Manufacturing” AND “Hepatitis C”	1	0
	“Drug Manufacturing*” AND Tuberculosis AND Challenges	1	1
	“Drug Manufacturing” AND “Hepatitis C” AND Challenges	0	0
	“Drug Distributions*” AND Tuberculosis AND Challenges	15	12
	“Drug Distributions*” AND “Hepatitis C” AND Challenges	8	5
	“Resource Limited Settings” AND Challenges AND Tuberculosis	97	58
	“Resource Limited Settings” AND Challenges AND “Hepatitis C”	18	15
	“Patient safety” AND Tuberculosis AND “Developing Countries”	17	10
	“Patient safety” AND “Hepatitis C” AND “Developing Countries”	19	9

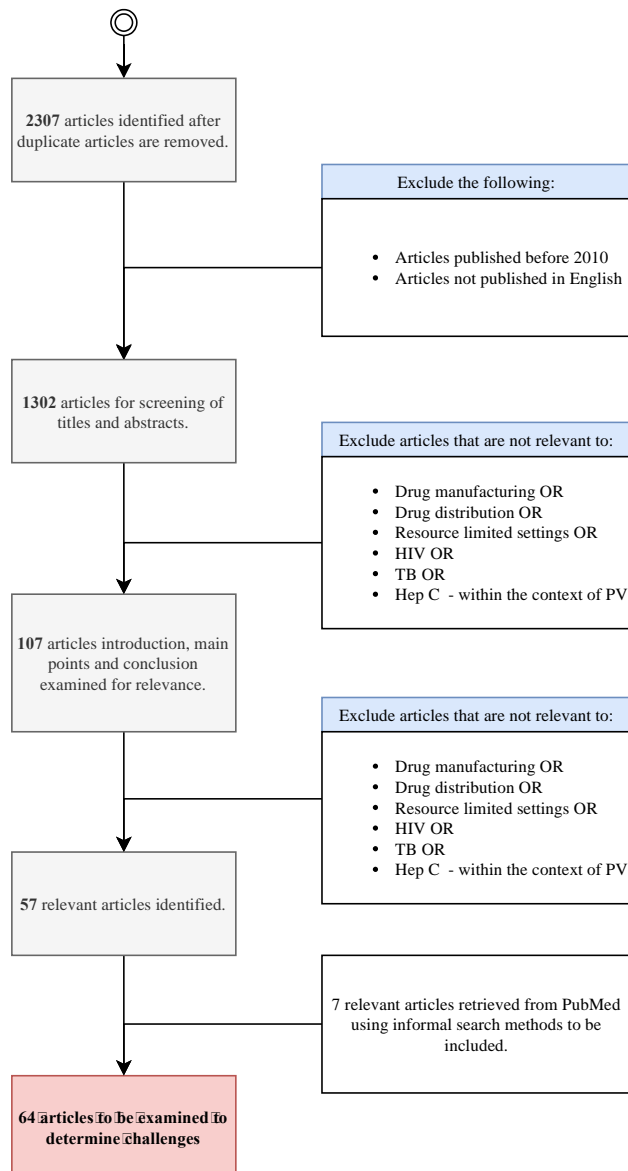


Figure 3.2: Systematic literature review process pertaining to (i) the MPP, (ii) HIV, TB and Hepatitis C, (iii) RLS challenges within context of a PV system

3.2.2 Results of systematic literature review

During the systematic literature review, the following 22 challenges relating to either or a combination of (i) the MPP, (ii) HIV, TB and Hepatitis C, and (iii) RLS within the context of PV systems were identified as:

- i. Adverse drug reactions;
- ii. Co-infections;
- iii. Counterfeit drugs;
- iv. Diagnostic testing;
- v. Dissatisfaction with healthcare system;

- vi. Drug adherence;
- vii. Drug dosages;
- viii. Drug-drug interactions;
- ix. Drug quality;
- x. Drug resistance;
- xi. Drug shortages;
- xii. Drug stock-outs;
- xiii. Drug supply system;
- xiv. Laboratories;
- xv. Lack of awareness & knowledge;
- xvi. Lack of reporting;
- xvii. Late initiation;
- xviii. Mislabelling of drugs;
- xix. Record keeping;
- xx. Specialised drugs;
- xxi. Substandard drugs; and
- xxii. Traditional medicines.

For a more detailed overview of the occurrence of these challenges in the documents, refer to Appendix B.

Within the context of this research inquiry, these challenges refer to concepts of concern that negatively impact the healthcare environment, especially relating to patient safety, and they are associated with one or more or a combination of the niche factors, (i) the MPP, (ii) HIV, TB and Hepatitis C, and (iii) RLS. As this research study investigates a context-specific PV system, these challenges must be considered within the context of PV and drug safety monitoring. These identified challenges are not necessarily directly related to PV systems, but they could, within the context of MPP drug provision systems, have an impact on drug safety monitoring and PV.

Furthermore, when considering the challenges listed above, and the challenges pertaining to traditional PV systems (see Chapter 2), it can be seen that similar challenges relate to both these instances. For example, ADR detection, which is associated with traditional PV systems, is similar in nature to the challenges Adverse drug reactions, listed above as (i), and the PV culture that is identified as a challenge within the context of traditional PV systems, see Section 2.3.4, is similar to a lack of awareness and knowledge, listed as (xv).

The 22 factors that were identified in the systematic review have an impact on the pharmaceutical and healthcare systems. These challenges are defined and explained in the following sub-section.

3.2.3 Adverse drug reactions

According to the WHO, an ADR is defined as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function” (Angamo *et al.*, 2016; Tetteh *et al.*, 2016). ADRs were found to pose a challenge in traditional PV systems (see Section 2.3.7); however it is also related to the MPP and RLS, as it has been found that inadequate drug manufacturing in RLS contributes to an increase in ADRs (Angamo *et al.*, 2016; Tetteh *et al.*, 2016).

ADRs can moreover affect the treatment process and have a negative impact on a patient’s quality of life, especially for HIV infected patients on ART (Manickum and Suleman, 2012; Masenyetse, Manda and Mwambi, 2015; Syed *et al.*, 2015; Angamo *et al.*, 2016; Mouton *et al.*, 2016; Tetteh *et al.*, 2016). Serious ADRs often causes patients to stop taking drugs, leading to a failure of drug adherence or treatment; it can also lead to patients being readmitted to hospital, thus placing an extra burden on the healthcare system, especially in the case of RLS (Manickum and Suleman, 2012; Angamo *et al.*, 2016; Tetteh *et al.*, 2016). It has also been determined that many reported ADRs are in fact preventable, which justifies the need for improving PV systems. Furthermore, through the MPP, multiple drug manufacturers are able to produce generic drugs and new fixed-dosage combinations, making it critical that ADRs are monitored carefully (Cox, 2001).

3.2.4 Co-infections

Co-infections are defined as simultaneous infection by multiple pathogenic species (Easterbrook, Sands and Harmanci, 2012). In the context of this research inquiry and in the relevant literature, co-infections are frequently documented in HIV, TB and Hepatitis C (e.g. between HIV and Hepatitis C, or between HIV and TB), especially in RLS (Miyano *et al.*, 2013; Marais and Schaaf, 2019).

It is also found that poor communication in the healthcare system leads to problems in referrals, monitoring and understanding of co-infections, thus increasing the disease burden of HIV, TB and Hepatitis C (Venkatesh *et al.*, 2011). Furthermore, the late initiation of treatments, especially in the case of co-infection, is often due to limitations in the diagnostic or screening process, with respect to HCP inadequately identifying and assessing the diseases (WHO, 2018b).

3.2.5 Counterfeit drugs

According to the WHO, counterfeit or falsified drugs are described as: “medical products that deliberately/fraudulently misrepresent their identity, composition or source” (Johnston and Holt, 2013). The WHO also state that counterfeit drugs can be branded or generic drugs containing the incorrect ingredients, no correct ingredients at all, or inadequate amounts of active ingredients, or they may be falsely packaged (Maponga *et al.*, 2007). When patients receive and take counterfeit drugs, their health may be compromised, or they may be put at risk to develop ADR or drug resistance (Maponga *et al.*, 2007; Nsimba, 2009; Miller, Nwokike and Stergachis, 2012; Djobet *et al.*, 2017). Counterfeit drugs are often a concern in areas where there is a shortage of drugs or where unregistered drug manufacturing and distribution systems are in place (Siva, 2010; Purohit *et al.*, 2015; Easterbrook *et al.*, 2017).

3.2.6 Diagnostic testing

With certain diseases, such as the three under consideration in this research study, diagnostic testing forms an integral part of diagnosing and monitoring the illness (Dominique *et al.*, 2015; Purohit *et al.*, 2015; Easterbrook *et al.*, 2017). However, it has been found that, in RLS, the infrastructure for diagnostic testing is not up to standard, i.e. accuracy, accessibility and cost-efficiency, which subsequently affects the prevention and monitoring systems related to these diseases (Purohit *et al.*, 2015). A delay in correct diagnosis can further increase the transmission of the disease in the community (Sands and Hons, 2012). Furthermore, the challenge of co-infections, for instance between HIV and TB, or HIV and Hepatitis C, and their diagnostic testing and identification, should also be considered when setting up testing facilities (Muhamadi, Nsabagasani and Nazarius, 2010; Bezabhe *et al.*, 2014; Busza *et al.*, 2018).

3.2.7 Dissatisfaction with healthcare system

The support, integrity and confidentiality of the HCP have a significant impact on the efficacy of treatment; it has been found that HIV patients' distrust or dissatisfaction with the healthcare system can lead to challenges, such as the late initiation of treatment or a failure in drug adherence, which often results in drug resistance or treatment failure (Houston, 2002). Thus the compassion and support of HCP are important to ensure that patients follow through with treatment (Bezabhe *et al.*, 2014).

3.2.8 Drug adherence

Drug adherence is when patients follow the recommendations made regarding the dosage, timing and frequency of medication in order for treatment to be effective (Bezabhe *et al.*, 2014). With regard to HIV, for example, a 95% of drug adherence is required in order to ensure that patients do not develop resistance or treatment failure (Oguntibeju, 2012; Syed *et al.*, 2015; Tetteh *et al.*, 2016). From the literature consulted it is evident that non-adherence in treatment is often attributed to the occurrence of ADRs (Maponga *et al.*, 2007; Bezabhe *et al.*, 2014; Syed *et al.*, 2015). In developing countries, other aspects that contribute to non-adherence are dissatisfaction with the healthcare system, perceived stigmas, lack of proximity to clinics, limited social support, poor record keeping, poor attitude of healthcare workers and certain personal factors (Haberer *et al.*, 2017). A study by Fontanarosa and Christiansen (2007) does, however, indicate that adherence can be improved with peer counselling and education (Fontanarosa and Christiansen, 2007).

3.2.9 Drug dosages

According to the American Medical Association, a dosage is defined as the prescribed administration of the amount, number and frequency of a specific drug over a period of time (Arnum, 2013). When considering drug safety monitoring within the context of the quality of a drug, ensuring that patients receive the correct dosages is imperative (Phelps and Rakhmanina, 2011). According to the literature, ensuring that patients receive the correct dosages is challenging, especially when considering paediatrics. Taking an incorrect dosage of a drug can lead to there being an inadequate number of drugs to fight the virus (Phelps and Rakhmanina, 2011). In paediatrics cases, when tablets are split, it results in asymmetry, which

subsequently results in unproportioned dosages of the drug being administered. Furthermore, it cannot be assumed that the ingredients are evenly distributed throughout a tablet, and thus pill splitting is not recommended (U.S. Department of Health and Human Services, 2019).

Consequently, when considering the MPP, and the opportunity to conduct R&D with respect to the development of context-specific drugs, i.e. paediatrics drugs, drug dosages need to be taken into account to ensure that quality of drugs within these settings.

3.2.10 Drug-drug interactions

Drug-drug interactions are defined as changes in the effect of the drug when it is taken in combination with another drug, which often result in the development of ADRs (Chen *et al.*, 2015; Winston and Underwood, 2015; Masuka *et al.*, 2018). The literature reviewed shows that drug-drug interactions are a frequent occurrence brought on by co-infections related to the diseases being investigated herein (Maponga *et al.*, 2007).

Drug-drug interactions can lead to other challenges, such as poor drug adherence or ADR (Prueksaritanont *et al.*, 2013), and can reduce the effectiveness of a drug. Furthermore, drug-drug interactions have been found to be a leading cause of drugs being withdrawn from the market (Houston, 2002; Stevens *et al.*, 2014; Djobet *et al.*, 2017).

3.2.11 Drug quality

Ensuring that the drugs that patients take are safe and effective is one of the priorities of the pharmaceutical industry with respect to PV systems, and it needs to be addressed continuously throughout the pharmaceutical value chain, from drug manufacturing, to distribution and patient monitoring (Kremzner, 2016). There are many different factors, such as a lack of good manufacturing practices (GMP), a lack of effective quality monitoring and the existence of poor drug plant characteristics that may contribute to the manufacturing of low quality drugs (Houston, 2002; Stevens *et al.*, 2014; Djobet *et al.*, 2017). It has been found that, in RLS in particular, the quality of drugs is often inconsistent and thus highlights the need for the implementation of effective quality control, especially where generic drug manufacturers are part of the pharmaceutical supply chain within the context of the MPP (Miller, Nwokike and Stergachis, 2012). Generic drug manufacturing and the production of fixed-dosage combinations challenge the existing drug quality management system (Maponga *et al.*, 2007; Keiser, 2010).

3.2.12 Drug resistance

Drug resistance is when the response to a drug in a susceptible population decreases significantly (Houston, 2002; Bertagnolio *et al.*, 2018; Wallis *et al.*, 2018). According to studies done by the WHO, it was found that treatment failure is often attributed to drug resistance; for example, in 2010, the prevalence of HIV drug resistance for patients starting treatment was rated at 6.8% and these patients were found most likely to fail their treatment (Easterbrook, Sands and Harmanci, 2012). Furthermore, it has also been documented that, due to co-infections, cross-resistance between drugs used for the treatment related to HIV, TB and Hepatitis C has become more prevalent (WHO, 2016).

3.2.13 Drug shortages

A drug shortage is defined by the WHO as the insufficient supply of medication or health products to meet the public and patients' needs (Wechsler, 2016). Drug shortages are often associated with smaller generic companies with little redundant capacity, which poses complications in situations with production problems (Jaskot *et al.*, 2011). Furthermore in literature it is argued that if possible drug suppliers were investigated and approved at a faster rate, it may lead to the mitigation of drug shortages (Wechsler, 2016; WHO, 2016).

3.2.14 Drug stock-outs

According to the WHO, a drug stock-out is defined as the absence of a medication that has been identified as essential at the point of service delivery (Pasquet *et al.*, 2010; Nilseng *et al.*, 2014). Drug stock-outs are often the result of poor infrastructure and insufficient human resources (Tassie, Bertagnolio and Souteyrand, 2011; Fokam *et al.*, 2013; MSF *et al.*, 2016). It has been reported that one third of countries globally struggle with drug stock-outs, which increases the risk of treatment failure and drug adherence (Tassie, Bertagnolio and Souteyrand, 2011). In order to insure that stock-outs do not occur, it is critical that planning and rational forecasting processes are in place (Maponga *et al.*, 2007; Nsimba, 2009).

3.2.15 Drug supply system

In developing countries, drug supply has often been a challenge, especially when considering the particular diseases within the context of this research inquiry, i.e. (i) HIV, (ii) TB and (iii) Hepatitis C. The treatment of these diseases requires a strict regime, in order to be effective (Maponga *et al.*, 2007; Steyn *et al.*, 2008). Furthermore, when limited amounts of drugs are available, ethical issues often arise with regard to how the medication should be prioritised for different patients (Nsimba, 2009; Nilseng *et al.*, 2014). Delays in drug delivery in RLS are often affected by poor infrastructure, such as poor roads, and financial burdens, such as a lack of funding for fuel (Steyn *et al.*, 2008). Challenges posed by a poor drug supply relate to all aspects of the supply chain, from ordering systems and storage of drugs to their distribution. According to the literature, ineffective drug supplies, which often result in drug shortages or stock-outs, are attributed to ineffective communication between national authorities, such as provincial districts, and healthcare provision facilities, or between the patients and the provision facilities (Easterbrook *et al.*, 2017).

3.2.16 Laboratories

When considering RLS and the three diseases focused on in this research, one of the challenges is the limited number of laboratories and testing infrastructures (Dominique *et al.*, 2015). Furthermore, laboratory systems are often faced with challenges with regard to quality control, connectivity and record keeping, which further influence diagnostic testing (Dominique *et al.*, 2015). The quality of the testing may also be affected by challenges, such as regular stock-outs, untrained staff and ineffective equipment (Fitzgibbon and Wallis, 2014). Laboratories often lack well-written standard operation procedures and good clinical laboratory practices (Purohit *et al.*, 2015). In a healthcare setting, especially when considering RLS in which there is a high burden of diseases, it is important for HCP to have the right knowledge on how to perform diagnostic testing to insure that the laboratory is not over-capacitated (i.e. reducing the

pressure placed on laboratories by having HCP perform diagnostic testing) (Easterbrook *et al.*, 2017; Marais and Schaaf, 2019).

3.2.17 Lack of awareness & knowledge

A particular challenge faced within the healthcare landscape is the lack of knowledge and awareness of the disease burden with respect to three prevalent diseases examined in this research. This lack of awareness entails a lack of understanding of these disease as well as a lack of knowledge of possible treatments (Easterbrook *et al.*, 2017). This aggravates other challenges, such as the lack of effective diagnostic testing or poor patient adherence to treatment (Easterbrook, Sands and Harmanci, 2012). Furthermore, there may also be a lack of effective drug safety reporting, which is important in a PV culture (see Section 2.3.4). (Ampadu *et al.*, 2016).

3.2.18 Lack of reporting

The lack of ADR reporting is a challenge that has already been identified in Chapter 2 with reference to traditional PV systems; however the situation may be worse in RLS (Ampadu *et al.*, 2016).

According to the literature, limited healthcare resources contribute to a lack of reporting of (Olsson *et al.*, 2010; Tassie, Bertagnolio and Souteyrand, 2011; Angamo *et al.*, 2016). In most low- and middle income countries, there is also inadequate legislation regarding the mandatory reporting of ADRs by HCP (Angamo *et al.*, 2016). Furthermore it has been found that under-reporting of ADRs in RLS is often caused by inadequate education of HCP relating to the identification and reporting of ADRs (Ford, Calmy and Mills, 2011).

3.2.19 Late initiation

The need to ensure that patients start treatment during the early phases of the disease is just as important as ensuring patients receive treatment (Muhamadi, Nsabagasani and Nazarius, 2010). It has however been found that, in RLS, treatment programs related to HIV, TB and Hepatitis C are not initiated early enough, often due to a lack of effective diagnostics (Muhamadi, Nsabagasani and Nazarius, 2010; Dominique *et al.*, 2015; Purohit *et al.*, 2015; Easterbrook *et al.*, 2017). This is often caused by inadequate healthcare infrastructures, i.e. limited human resources, delay in diagnostics, or socio-economic factors, such as misconceptions about the treatment (Arnum, 2013). Furthermore, these socio-economic factors are closely related to the factor of dissatisfaction with the health system (see Section 3.2.7).

3.2.20 Mislabelling of drugs

Mislabelling of drugs can have severe impacts on a patient's safety and health but not only in the context of PV systems, but generally (Arnum, 2013). In RLS contexts, in particular, mislabelling of drugs are more prevailing (WHO, 2007a; Djobet *et al.*, 2017). According to the WHO, drug labels need to contain the name and amount of the active ingredients, the batch number of the manufacturer, the expiry date, the name and the address of the manufacturer; moreover, any required storage and usage directions must be clearly indicated (World Health Organization, 2007a; Djobet *et al.*, 2017).

3.2.21 Record keeping

Patient health records are essential to HCP, as they contain vital patient information, such as unique patient identifiers and medical histories. Health records track a patient's health information to facilitate follow-up and to keep track of the treatment process and outcomes (Olsson *et al.*, 2010; Fokam *et al.*, 2013). However, in RLS, effective record keeping is often lacking or absent (Bezabhe *et al.*, 2014). Patients' records are often lost, resulting in patients having to repeat certain medical procedures unnecessarily (Phelps and Rakhmanina, 2011; Dahinten *et al.*, 2016).

3.2.22 Specialised drugs

In developing countries, which are often associated with having limited resources, the development of context-specific drugs with respect to population groups or disease burdens are becoming prevalent. Furthermore, these drugs are often have associated with low-quality control systems and thus require even more effective drug safety monitoring (Dahinten *et al.*, 2016).

Two examples of this are the prevailing use of traditional medicines and the use of paediatric drugs to treat HIV (Phelps and Rakhmanina, 2011; Dubrocq, Rakhmanina and Phelps, 2017). The need for paediatric drugs is much higher in low-middle income countries, as it has been found that, in developed countries, mother-infant transmission has been reduced effectively (Phelps and Rakhmanina, 2011). Furthermore, the use of adult ART for children is actually ineffective, as children absorb and metabolize drugs differently to adults (Phelps and Rakhmanina, 2011; Dubrocq, Rakhmanina and Phelps, 2017). Through the MPP, drug manufacturers can develop innovative fixed-dosage combinations specifically for paediatric use; however, when developing paediatric drugs, the palatability, taste, size, dosages, formulation and ease of handling or administration of the drugs should be considered (WHO, 2018b).

3.2.23 Substandard drugs

The WHO defines substandard drugs as: “authorized medical products that fail to meet either their quality standards or specifications, or both” (Djobet *et al.*, 2017). A drug is regarded as a substandard drug if it contains too much or too little active ingredients in comparison to the formulation specifications (Johnston and Holt, 2013; Djobet *et al.*, 2017). Substandard drugs are often attributed to poor manufacturing and distribution systems with unqualified personnel and inadequate control systems (Kisangau *et al.*, 2007; Johnston and Holt, 2013).

3.2.24 Traditional medicines

It has been found that, in RLS in particular, there is an increasing production and usage of traditional medicines for the purpose of treating diseases. Traditional medicines are skills and practices based on indigenous cultural beliefs and theories, which are used to prevent, diagnose, improve and/or treat health related issues (Kisangau *et al.*, 2007; Perampaladas *et al.*, 2010). The increase in production of these medicines is, however, resulting in challenges with regard to quality control, although intercultural standards are already being developed for traditional medicines (Perampaladas *et al.*, 2010; Sahoo and Manchikanti, 2013; Kloos, 2017). Aspects to consider with regard to quality control of such traditional medicines are, for

example, the type and quality of the raw materials used, and the knowledge of the manufacturers regarding quality monitoring processes, as well as the lack of general drug safety related processes (Kankhar, 2006).

3.2.25 Discussion of challenges related to Medicine Patent Pool, HIV, TB and Hepatitis C, and resource limited settings

After contextualising the 22 challenges discussed above it was found that certain relationships exist between some of the identified challenges, i.e. the challenges may relate to one another, aggravate or even alleviate each other. In order to gain a better understanding of these relationships, a challenges landscape was developed (see Section 3.4 below), as had been done in Chapter 2 in relation to traditional PV systems.

However, when considering these challenges, it is clear that they are not only related to the PV system but to the broader context of the pharmaceutical value chain. Thus, in order to gain a systems perspective understanding of these relationships between the challenges and the pharmaceutical value chain, the envisaged challenges landscape will consider the context of the entire pharmaceutical value chain and not only the context of drug safety monitoring.

3.3 PHARMACEUTICAL VALUE CHAIN

From the literature related to the pharmaceutical landscape, it can be deduced that the pharmaceutical value chain has three main components, namely, the manufacturing of the drugs, the final product, and the distribution of the drugs or products (European Union, 2013). Drug safety monitoring should be included throughout the entire pharmaceutical value chain, as it has been seen that innovative modes of drug supply, such as the MPP, not only affect manufacturing and distribution but also patient monitoring (Kankhar, 2006; UNITAID, 2010; European Union, 2013). Thus, in the context of this dissertation, the pharmaceutical value chain is considered to have four phases: (i) supply, (ii) distribution, (iii) final product, and (iv) the health system, which refers to patient usage and drug monitoring (Dahinten *et al.*, 2016).

Within the context of this research inquiry, the drug supply is sub-divided into the process of R&D and the process of manufacturing, where R&D relates to any form of investigation conducted with regard to drugs, and manufacturing refers to the process of developing these drugs. Distribution refers to the processes associated with the transporting of the drugs after manufacturing to the required healthcare facility. The third phase, i.e., the final products, refers to the actual drug that is accessible at the healthcare facility. The last phase, the healthcare system, is subdivided into the processes of patient usage and monitoring. Patient usage refers to the process of providing the final product to the patient, while monitoring refers to the drug safety monitoring process to ensure patient safety monitoring (Kankhar, 2006; UNITAID, 2010; European Union, 2013; Dahinten *et al.*, 2016).

In order to gain a systems perspective understanding of the relationships between the identified challenges, as listed in Section 3.2, and the above described pharmaceutical value chain within the context of the MPP drug provision systems, a challenges landscape is developed. This is discussed in the following section.

3.4 OVERVIEW OF CHALLENGES LANDSCAPE OF MEDICINE PATENT POOL, HIV, TB AND HEPATITIS C, AND RESOURCE LIMITED SETTINGS

As emerged from a discussion of the challenges associated with the traditional PV system in Chapter 2, here too it was found that the challenges relating to the niche factors, (i) the MPP, (ii) HIV, TB and Hepatitis C, and (iii) RLS do possibly relate to one another; furthermore, they may also have (possibly different) impacts on the respective stages of the pharmaceutical value chain. Thus, an additional challenges landscape is developed to gain a holistic view of these.

The development methodology of the challenges landscape is discussed in the following subsection. The challenges landscape is then discussed from three perspectives below: firstly, the relationships between the various challenges are considered and presented in a relationship diagram; secondly, the relationship diagram, the pharmaceutical value chain framework and the various challenges are amalgamated and presented in a schematic representation of the challenges landscape; and, thirdly the schematic representation of the challenges landscape is discussed.

3.4.1 Challenges landscape development methodology

A similar approach was followed here as had been used in Chapter 2 to develop the challenges landscape related to traditional PV systems. Firstly, based on the discussion of the challenges it could be deduced that many of the challenges are inter-related with each other and with the different phases of the pharmaceutical value chain. Thus, in order to gain a better understanding of these relationships, a relationship diagram was developed, indicating which challenges relate to one another.

Using the insights gained from the development of this relationship diagram, the challenges could be grouped together based on shared or similar attributes and according to their impact on the pharmaceutical value chain. From this it was deduced that there were three overarching groups of challenges with respect to the pharmaceutical value chain: (A1) – inadequate manufacturing and distribution systems challenges, (A2) – quality related challenges, and (A3) – ineffective drug safety monitoring systems. Within these groups there were subsets, which will be discussed in more detail in Section 3.4.3.

3.4.2 Relationship diagram

Figure 3.3 illustrates the respective relationships between the challenges. The relationships are based on: (i) challenges that share common attributes or characteristics, and (ii) challenges that affect one another by either aggravating or alleviating each other. These relationships and correlations were not necessarily explicitly mentioned in the literature but emerged after synthesising the information gathered through the systematic literature review. The relationships, indicated in Figure 3.3, are grouped in such a manner as to indicate the impact that a relationship has on a specific section of the pharmaceutical value chain. In the case where a relationship has an impact on more than one phase, both are indicated.

	ADR	Drug adherence	Quality	Lack of reporting	Record Keeping	Counterfeit Drugs	Drug-drug Interactions	Drug Supply	Later ART initiation	Substandard Drugs	Dosages	Drug resistance	Drug stock-outs	Paediatric drugs	Specialized Drugs	Traditional Medicine	Drug shortages	Dissatisfaction with health system	Labelling
ADR				X			X												
Drug adherence				X	X			X				X	X				X	X	X
Quality						X				X									
Lack of reporting																			
Record Keeping									X										
Counterfeit drugs												X							
Drug-drug interactions																X			
Drug supply												X	X				X		
Later ART initiation																		X	
Substandard drugs																			
Dosages																			
Drug resistance													X				X		
Drug stock-outs																	X		
Paediatric drugs																			
Specialized Drugs																			
Traditional Medicine																			
Drug shortages																			
Dissatisfaction with health system																			
Labelling																			

Key	
Drug development	
Manufacturing	
Distribution	
Product	
Patient usages	
Monitoring	

Figure 3.3: Relationship diagram for MPP, disease burden associated with MPP and RLS challenges landscape

3.4.3 Challenges landscape related to the Medicine Patent Pool, HIV, TB and Hepatitis C and resource limited settings

Once the relationships between the different challenges at the irrespective phases of pharmaceutical value chain had been established, a graphical synthesis of the challenges landscape was developed. This graphical landscape is presented in Figure 3.4.

As stated, three overarching groups of challenges were identified, namely: (A1) – challenges due to inadequate manufacturing and distribution systems, (A2) – challenges due to quality issues in drug manufacturing and distribution, and (A3) – challenges related to inadequate drug safety monitoring systems. In Figure 3.4 these groups are denoted as A1, A2, and (A3). In group (A1), there are five sub-groups: (A1.1) refers to challenges associated with specialised drugs; (A1.2) to challenges due to an inadequate drug supply; (A1.3) to challenges within the context of drug-drug interactions; (A1.4) to challenges relating to drug resistance, and (A1.5) to inadequate laboratory and diagnostics testing. In group (A2), there are two sub-groups relating to inadequate quality systems: (A2.1) are the challenges relating to drug manufacturing, while (A2.2) are the challenges relating to the physical drug or product. (A3) did not have any sub-groups, as the related challenges were found to all form part of the universal group under monitoring. Table 3.2 below explains these different groups.

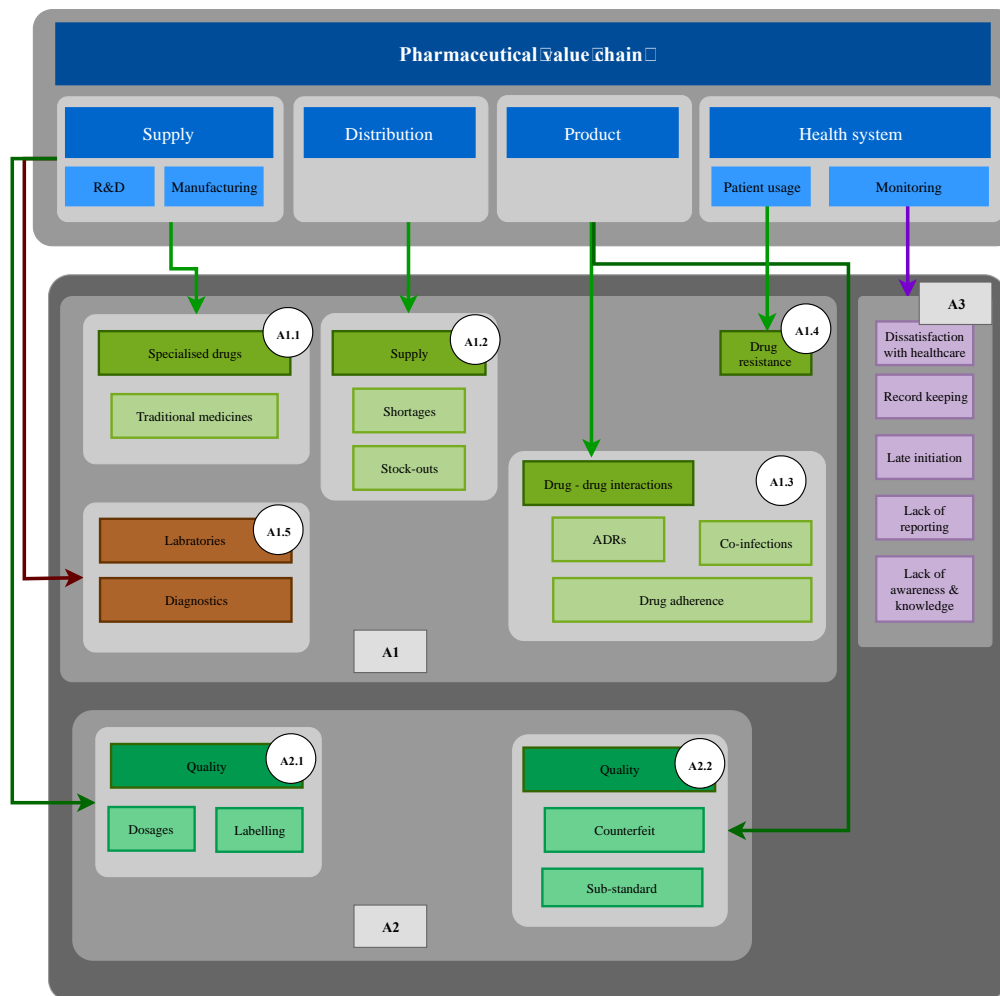


Figure 3.4: Challenges landscape related to (i) the MPP, (ii) HIV, TB and Hepatitis C, and (iii) RLS

Table 3.2: MPP, RLS and groupings relating to the challenges landscape of specific diseases

Challenges group	Sub-group	Challenges	Explanation
A1	A1.1.	Specialized drugs, paediatric drugs, traditional medicines	In RLS the development and manufacturing of drugs often requires the creation of drugs for the specific needs of patients, referred to as specialized drugs. For this research inquiry, the two cases of specialized drugs are paediatric drugs and traditional medicines (Maponga <i>et al.</i> , 2007; Phelps and Rakhmanina, 2011). These challenges mostly appear during the phases of drug development and manufacturing. Furthermore, traditional medicines often have an impact on drug-drug interactions (Steyn <i>et al.</i> , 2008).
	A1.2.	Drug supply, drug shortages, drug stock-outs	Within the drug distribution side of the value chain, drug supply in the low- and middle-income countries is one of the major concerns; it is further affected by the limited resources of these settings. As mentioned, there are many factors that affect drug supply, from poor infrastructure to factors in the supply chain, such as ordering systems (Fokam <i>et al.</i> , 2013). The problems in drug supply lead to drug shortages and drug stock-outs. These in turn lead to difficulties with regard to patient safety, since shortages and stock-outs are often the causes of drug resistance in patients and poor adherence (Maponga <i>et al.</i> , 2007).
	A1.3.	Drug-drug interactions, ADR, drug adherence	Of the identified challenges, drug-drug interactions arise in the final product stage of the value chain. Co-infections related to HIV, TB and Hepatitis C often require that drugs are taken in combination with other drugs, which can lead to negative drug-drug interactions. It has also been identified that traditional medicines, which are often used in RLS, have an effect on drug-drug interactions (U.S. Department of Health and Human Services, 2019). Drug-drug interactions often cause serious side-effects and ADRs (Bezabhe <i>et al.</i> , 2014). ADRs often have an effect on a patient's treatment process, as serious ADRs can affect a patient's adherence to the treatment, since they often stop taking their medications due to ADRs (Ford, Calmy and Mills, 2011; Fokam <i>et al.</i> , 2013). This inevitably affects not just the patient but the community as a whole. Drug adherence implicates the value chain in both the final product stage and the patient usage stage.
	A1.4.	Drug resistance	Drug resistance is one of the challenges associated with the patient's usage of certain drugs. Many factors can lead to drug resistance such as, drug delivery, shortages and stock-outs as well as drug adherence (Muhamadi, Nsabagasani and Nazarius, 2010; Bezabhe <i>et al.</i> , 2014). Furthermore, drug resistance is also caused by inadequate drug monitoring systems, such as the poor integrity of the health system and weak record keeping (Dominique <i>et al.</i> , 2015; Purohit <i>et al.</i> , 2015; Easterbrook <i>et al.</i> , 2017).
	A1.5	Laboratories, diagnostics	In RLS the challenges of inadequate infrastructures and limited numbers of laboratories result in limited diagnostic testing, which further burdens the healthcare system; it can also increase disease transmission (Dominique <i>et al.</i> , 2015). Furthermore the quality of the testing is also affected by challenges, such as regular stock-outs, untrained staff and ineffective equipment (Stevens <i>et al.</i> , 2014; Djobet <i>et al.</i> , 2017).

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Challenges group	Sub-group	Challenges pertaining to	Explanation
A2	A2.1	Quality, dosages, labelling	The quality challenges identified have an impact on the supply side of the value chain. Drug manufacturing companies have to have quality systems in place to ensure that the drugs are safe and effective, and that will not harm patients (Phelps and Rakhmanina, 2011). Insufficient quality systems in drug manufacturing companies manifests in mis-labelling and wrong drug dosages. If drug manufacturing companies do not have quality systems in place, drug dosages may be inadequate or incorrect, with ingredients not distributed evenly, for instance, and labels being incorrect (WHO, 2007a). This causes problems with regard to patient safety (Miller, Nwokike and Stergachis, 2012; Djobet et al., 2017).
	A2.2	Quality, counterfeit drugs, sub-standard drugs	The quality of the final product is affected by ineffective manufacturing and distribution systems (Maponga et al., 2007). It may lead to poor-quality, counterfeit or sub-standard drugs. These challenges are mostly brought on by a lack of quality in the drug supply process and can seriously affects patient safety. Furthermore, counterfeit drugs often lead to serious ADR or drug resistance (Nsimba, 2009; Miller, Nwokike and Stergachis, 2012; Djobet et al., 2017), (Muhamadi, Nsabagasani and Nazarius, 2010).
A3		Integrity of the health system, record keeping system, late ART initiation, poor health systems, lack of awareness, lack of reporting	In the final stage of the drug value chain, namely monitoring, many challenges arise, often due to limited resources. The integrity of the health care system and the lack of effective record keeping are two of the contributing factors for the late initiation of treatment. This can be very detrimental to patient care and often leads to unnecessary deaths. Furthermore, the lack of effective record keeping and patient dissatisfaction with the health care systems affects drug adherence, which again leads to drug resistance (Angamo et al., 2016). The lack of reporting is one of the major challenges in RLS during the monitoring stage of the value phase. Preventable ADRs are often under-reported, which leads to further complications, such as a lack of drug adherence and an increase in drug resistance (Easterbrook, Sands and Harmanci, 2012). Furthermore the lack of awareness related to the disease, HIV, TB and Hepatitis C all contribute to ineffective diagnostic processes and a lack of reporting (Aranda-Jan, Mohutsiwa-Dibe and Loukanova, 2014).

3.5 THE PHARMACEUTICAL VALUE CHAIN CHALLENGES LANDSCAPE

When considering the challenges landscape developed in this chapter, coupled with the challenges landscape related to traditional PV systems that was developed in Chapter 2, it can be seen that there are certain correlations and analogies that can be drawn, and thus they can be synthesised into an overarching challenges landscape that is applicable for the development of a decision support tool within the context of MPP drug provision systems.

After examining the different challenges created by the four niche factors, in other words, (i) traditional PV systems, (ii) the MPP, (iii) HIV, TB and Hepatitis C, and (iv) RLS, it was found that certain correlations and relationships exist between them. Thus, in order to gain a holistic view, the two challenges landscapes were synthesised together to develop an overarching landscape referred to as the “*Pharmaceutical Value Chain Challenges Landscape*” (PVCCL). This challenges landscape covers the entire pharmaceutical value chain from the drug manufacturing through the distribution phase to the drug safety monitoring phase (which includes the PV related process).

Given that the PVCCL was developed by merging the two previously developed challenges landscapes, the identified relationships and discussions of the groupings in Table 2.2 and Table 3.2 are still relevant within the context of the PVCCL. Furthermore, it was established that certain challenges in both the drug supply system and the PV system affect and relate to one another during certain stages of the pharmaceutical value chain. These different relationships are illustrated in Figure 3.5. The schematic representation of the PVCCL typology is provided in Figure 3.6. The seven identified groups are indicated by means of a colour key.

This overarching challenges landscape provides a system perspective understanding of the relevant challenges that should be taken into account when developing a decision support tool that facilitates the development of context-specific PV systems and the identified niche factors. In the following chapter the PVCCL will be investigated to determine what requirements need to be addressed when developing the proposed PV system.

		Supply and distribution										Diagnostics		Quality					Monitoring					PV culture	Lack of education				Stakeholders								Reporting & process										
		specialised drugs	Paediatric drugs	Traditional medicines	Supply	Shortages	Stock-outs	Drug-drug interactions	ADRS	Co-infections	Drug adherence	Drug resistance	Laboratory	Diagnostics	Quality	Dosages	Labelling	Counterfeit	Sub-standard	Integrity of the system	Record keeping	Late initiation	Lack of reporting		Awareness	Education	KAP	Training	Curriculum	Government	Limited resources	Lack of finances	Pharmaceutical companies	Doctors	Pharmacists	Consumers	Paediatric/pregnant	Traditional medicines	ADR detection	Confidentiality & ethics	Under reporting	Communication	Quality of data				
Supply and distribution	specialised drugs	X	X																																												
	Paediatric drugs														X					X						X								X			X										
	Traditional medicines							X	X						X							X			X											X			X								
	Supply					X	X			X	X						X								X					X	X	X	X														
	Shortages																	X																													
	Stock-outs																	X																													
	Drug-drug interactions									X	X	X	X												X					X	X	X	X														
	ADRS														X		X					X	X		X	X							X	X	X		X			X							
	Co-infections									X	X		X	X																																	
	Drug adherence										X									X	X																										
Drug resistance															X			X	X						X																						
Diagnostics	Laboratory																								X																						
	Diagnostics													X											X																						
Quality	Quality														X	X	X	X						X																						X	
	Dosages																																														
	Labelling																																														
	Counterfeit																																														
	Sub-standard																																														
Monitoring	Integrity of the system																				X																										
	Record keeping																																														
	Late initiation																																														
	Lack of reporting																																														
	Awareness																																														
Lack of education	PV culture																								X	X																					
	Education																								X	X																					
	KAP																																														
	Training																																														
	Curriculum																																														
Stakeholders	Government																																														
	Limited resources																																														
	Lack of finances																																														
	Pharmaceutical companies																																														
	Doctors																																														
	Pharmacists																																														
	Consumers																																														
	Paediatric/pregnant																																														
	Traditional medicines																																														
	ADR detection																																														
Reporting & process	Confidentiality & ethics																																														
	Under reporting																																														
	Communication																																														
	Quality of data																																														

Figure 3.5: Relationship diagram related to the pharmaceutical value chain challenges landscape

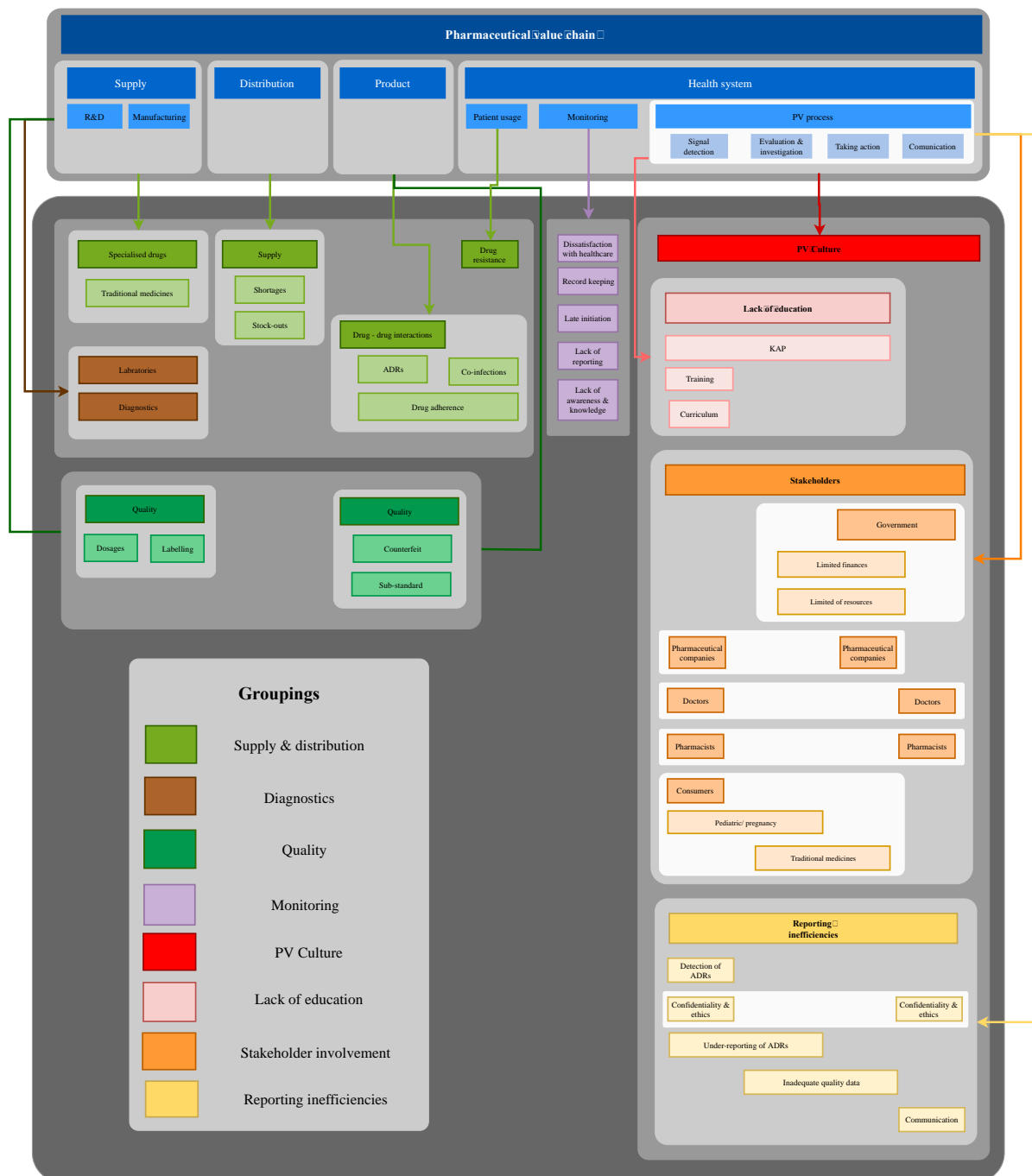


Figure 3.6: Typology of the pharmaceutical value chain challenges landscape

3.6 CHAPTER 3 CONCLUSION

In this chapter, the input identification phase of the systems engineering approach was concluded by contextualising and investigating the three remaining niche factors – in other words, the MPP, the MPP disease burden of HIV, TB and Hepatitis C, and RLS – in order to identify the challenges associated with these factors within the context of PV. A challenges landscape was developed, and then synthesised with the challenges landscape previously developed in Chapter 2 in relation to traditional PV systems, in order to develop an overarching challenges landscape that covers the entire pharmaceutical value chain - PVCCL.

In the following chapter, the next phase of the systems engineering approach, the requirement analysis, will be executed. During this phase, the PVCCL will be looked at closely in order to identify the requirements that will guide the development of a decision support tool.

Chapter 4: Requirement specification development

As previously outlined, this research inquiry follows a systems engineering approach to address the lack of an existing PV system that is aligned with and appropriate for MPP drug provision systems. The systems engineering approach used herein is a four-phase approach, as discussed in Section 1.4. In Chapter 2 and Chapter 3, the input identification phase was executed, which entailed contextualising the research problem by addressing the four niche factors and identifying the challenges associated with these factors in the context of drug safety monitoring. The identified challenges were synthesised to develop a challenges landscape, the PVCCL. However, in order to advise on a PV system that will effectively address and alleviate these challenges in the context of the MPP drug provision systems, a requirement specification for such a system needs to be developed.

Thus, in this chapter, the requirement specification that will guide the development of a decision support tool, will be developed. The process of developing said requirements specification is firstly discussed, which entails considering the developed PVCCL, and conducting systematic literature reviews pertaining to the niche factors. Thereafter, the developed set of requirement specifications is discussed, followed by a discussion of the verification process executed to confirm whether the developed requirement specifications would be satisfactory given the conditions of a context-specific PV system.

The requirement analysis phase of the research is illustrated in Figure 4.1, as well as how it relates to other phases of the research.

It should be noted that a substantial portion of this chapter has been published as an article in the Proceedings of the 25th ICE/IEEE International Technology Management ©IEEE. The article can be found in Appendix A, Section A.2.

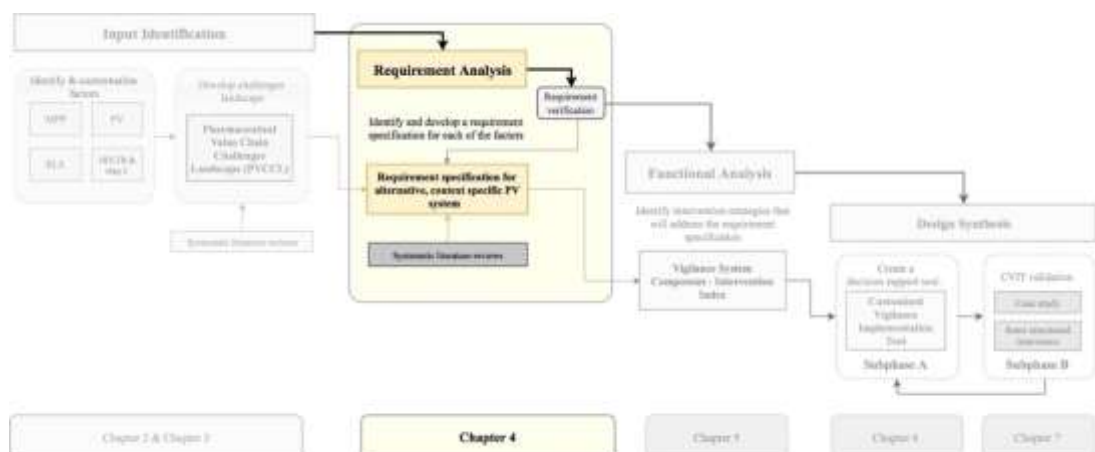


Figure 4.1: Systems engineering approach: Requirement analysis

4.1 REQUIREMENT ANALYSIS PHASE

As stated, the requirement analysis phase is the second phase in the systems engineering approach (United States Government, 2001). This phase entails identifying the functional requirements called for by the niche factors in designing a decision support tool for a context-specific PV system by addressing the challenges associated with these factors, and defining the specific requirements in the context of such a system (United States Government, 2001).

In this dissertation, a three-step approach was conducted during the requirement analysis in order to develop and verify a requirement specification. During the development phase, (i) systematic literature reviews were conducted to identify the requirements that would be called for by the niche factors in such a system, and (ii) the PVCCL was consulted to identify possible additional requirements. Systematic literature reviews were conducted in respect of each of the four niche factors, (i) traditional PV systems, (ii) the MPP, (iii) HIV, TB and Hepatitis C, and (iv) RLS, in order to identify documented requirements related to PV systems.

In 2010, the WHO was recruited by the Global Fund¹³ to develop a minimum set of requirements for a functioning PV system, in an attempt to assist countries that were seeking to improve their national PV centres (WHO and The Global Fund, 2010). However, these requirements were found to be inadequate when considering the context of this research inquiry. Thus, it was decided to conduct systematic literature reviews to identify whether there were any unique requirements related to the four niche factors that should be taken into consideration when developing a decision support tool that facilitates the development of context-specific PV systems.

Consulting the PVCCL entailed addressing the challenges identified with regard to the four niche factors to ensure that the proposed decision support tool would be able to address, alleviate and/or eliminate these challenges. Each of the groups of challenges, as described Chapter 3, was examined independently to determine if any additional requirements, which had not been identified during the systematic literature reviews, should be taken into account. If additional requirements were identified, they were synthesised to form a preliminary requirement specification.

Furthermore, a verification process was conducted to evaluate whether the preliminary requirement specification was satisfactory with respect to the conditions, i.e. challenges landscape, the niche factors call for in a context-specific PV system. This verification process was used to determine whether the identified requirements were acceptable within the context of this research inquiry, and to identify possible additional requirements that should be taken into account (the verification process is discussed in Section 4.5). After the necessary changes, adaptations and recommendations were integrated, a final requirement specification was developed, which is discussed in Section 4.6. These specifications will then be used as guiding and foundational principles for the development of a decision support tool that would facilitate the development of a context-specific PV system, which will be discussed in the following chapters.

¹³ The Global Fund is an international organization aimed at ending the disease burden of AIDS, TB and malaria as epidemics through partnering with governments, civil societies, the private sector and the public.

4.2 CONSULTING THE LITERATURE

As this dissertation considers a PV systems it is first necessary to identify the requirements such a system would have to fulfil. Furthermore, as this research study considers the environment of MPP drug provision systems, and consequently the niche factors (i) traditional PV systems, (ii) the MPP, (iii) HIV, TB and Hepatitis C, and, (iv) RLS, it is necessary to investigate the possible unique requirements these factors call for.

According to the WHO, (WHO and The Global Fund, 2010), there are five minimum requirements for an effective PV system:

- i. A national PV centre with designated staff members and a defined structure;
- ii. A national spontaneous reporting system with ADR reporting forms;
- iii. A system for collecting the ADR reports;
- iv. A PV advisory group that can provide technical assistance; and
- v. A clear communication strategy between the stakeholders involved.

However, when considering the challenges associated with the niche factors as discussed in Chapter 3 in relation to the PVCCCL, it can be assumed that the minimum requirements for a PV system are inadequate to address the requirements these niche factors would call for in a drug safety monitoring system. Thus, systematic literature reviews focused on each of the four identified niche factors (see Chapters 2 and 3).

In the following sub-section, each systematic literature review will be discussed, along with the identified requirements.

4.2.1 Systematic literature review related to traditional pharmacovigilance system requirements

The aim of this systematic literature review was to gain a better understanding of the PV requirements that have been documented in the literature and to identify any potential universal requirements relating to traditional PV. As was the case in the previous systematic literature reviews presented in Section 2.3.1 and Section 3.4.1, Scopus and PubMed were used as primary search databases. Using keywords¹⁴ related to PV, as indicated in Table 4.1, a total of 293 relevant documents were initially identified. To ensure that the most relevant documents were included, inclusion/exclusion criteria were applied, which entailed only including documents that were published in English and from 2000 onwards. After these initial criteria had been applied, a total of 262 documents remained for consideration; their abstracts of the documents were thus screened for relevance with regard to any requirements pertaining to traditional PV. Thereafter, 31 documents were found to be relevant; after each of these full articles had been reviewed, only 12 were found to be of value to the requirements identified in this study. Any duplicate documents found when conducting the search in PubMed were excluded, as they had already been included when conducting the search in Scopus.

¹⁴ It should be noted that, in the search protocol used with Scopus, W/5 (within 5 words) was used as an attempt to ensure that the requirements would be related to pharmacovigilance; however in PubMed W/5 is not identified as a search protocol and thus AND was used as a compromise.

Furthermore, Google Scholar was consulted for serendipitous findings and thus a further three articles were included as a result. In the end, therefore, a total of 15 documents were reviewed to identify the requirements that are universal to traditional PV systems.

Table 4.1: List of search terms used to identify traditional PV related requirements

Search base	Key words or phrases used	Initial number of documents	Number of documents after inclusion/exclusion criteria	Number of documents after abstract screening	Number of documents after final screening
Scopus	Pharmacovigilance W/5 requirements	76	54	21	7
PubMed	Pharmacovigilance AND requirements	194	176	14	5
Google Scholar	Serendipitous findings				3
Total number of documents		293	262	31	15

4.2.2 Requirements relating to traditional PV systems identified from the literature

After these 15 articles had been reviewed, 11 requirements pertaining to traditional PV systems were identified; they are described in the following sub-sections. For a detailed overview of the occurrence of each of these requirements in the documented literature, refer to Appendix B.

4.2.2.1 *Pharmacovigilance education as part of the health systems environment*

The literature calls for PV education to form a more vital part of the health system (WHO, 2002b, 2006b; Hanzl-Dujmović, Sulić-Milišić and Starešinić-Šernhorst, 2007; Khattri *et al.*, 2012; Zun, 2014; Olsson, Pal and Dodoo, 2015a; Nwaiwu, Oyelade and Eze, 2016; Olivier *et al.*, 2016). In a study done by the WHO and the Uppsala Monitoring Centre (UMC), the importance of integrating drug safety and PV into the medical health curricula is highlighted, as well as the lack of research and postgraduate training in this field. The research argues that, if healthcare practitioners were confident in their ability to correctly diagnose, manage and prevent ADRs, they would be more likely to report ADRs. Furthermore, when looking at PV education, all stakeholders should be actively involved, although the national PV centres and other similar establishments should be seen as the primary teaching bases. Also, it is argued in the literature that PV education should not be limited to training sessions but should include a variety of different methods, such as conferences, educational programmes and scientific publications (WHO, 2002b).

4.2.2.2 *Clear lines of communication within a pharmacovigilance system*

For a system to work and function effectively, clear lines of communication between all the different stakeholders are vital (WHO, 2002b, 2006b; Olsson, Pal and Dodoo, 2015a). Thus, in order for the proposed context-specific PV system to operate effectively, clear channels of communication would have to be formed between, for example, quality control labs and PV centres; government/regulatory bodies and PV centres; healthcare professionals and consumers (WHO, 2002b, 2006b; Olsson, Pal and Dodoo, 2015a). A clear communication strategy is also one of the WHO's minimum requirements for a functioning PV system (WHO and The Global Fund, 2010).

4.2.2.3 Patient involvement in the reporting of adverse drug reactions

In the literature it is argued that a PV system requires the involvement of patients with respect to the reporting of ADRs (Pietrek, Coulson and Czarnecki, 2009). Furthermore, patients should also receive feedback related to reported ADRs (WHO, 2006b).

4.2.2.4 Database for managing adverse drug reactions reports

The WHO states that one of the minimum requirements for an effective PV system is that a database for the collecting and the managing of ADRs needs to exist (WHO and The Global Fund, 2010). Although the success of a PV system requires the reporting of ADRs, its effectiveness will rely on the correct management of the data gathered and the quality of the databases (WHO, 2006b).

4.2.2.5 Pharmacovigilance centre or reporting system with designated staff

A well-structured PV system should consider all the stages of the system, from collecting and managing ADR reports and clinically evaluating these to taking regulatory action in response to reported ADRs and alerting prescribers, manufacturers and the public (WHO, 2006b; Pietrek, Coulson and Czarnecki, 2009; WHO and The Global Fund, 2010; Khattri *et al.*, 2012; Olsson, Pal and Dodoo, 2015a). Furthermore, a PV system requires designated, qualified staff as well as an advisory committee to assist with technical matters (WHO, 2006b; Olsson, Pal and Dodoo, 2015a; Nwaiwu, Oyelade and Eze, 2016).

4.2.2.6 Quality management and control systems to be integrated within pharmacovigilance

Quality management and quality control systems need to be integrated into the different steps of the PV system, i.e. from signal detection to evaluation and taking action (Olsson, Pal and Dodoo, 2015b). Good Pharmacovigilance Practices (GVP) state that quality management systems should include (i) clear policies, (ii) standard operating procedures, (iii) working instructions, and (iv) job descriptions with regard to drug safety (Pietrek, Coulson and Czarnecki, 2009). Furthermore, quality management also entails ensuring that the system is regularly reviewed and audited, and that the equipment used is regularly validated (Pietrek, Coulson and Czarnecki, 2009). All stakeholders involved with pharmacovigilance need to embrace the concept of quality control and to demonstrate collaborative, transparent, proactive behaviour with respect to the implementation of quality control (Pietrek, Coulson and Czarnecki, 2009; Olsson, Pal and Dodoo, 2015a; Nwaiwu, Oyelade and Eze, 2016).

4.2.2.7 Definition of stakeholders' roles

In the literature it is argued that, in order for a PV system to function effectively, all the different stakeholders involved, i.e. government, regulatory bodies, national PV centres, HCP, pharmaceutical companies and patients, must have clearly defined roles and responsibilities of which they are informed (Hanzl-Dujmović, Sulić-Milišić and Starešinić-Šernhorst, 2007; Khattri *et al.*, 2012; Nwaiwu, Oyelade and Eze, 2016). Furthermore, the national PV centre or other specified regulatory body (i.e. SAPRHA in the case of South Africa) is responsible for managing the databases collecting and evaluating the reports, identifying any suspicious reactions, and recommending specific regulatory actions (WHO, 2006b).

4.2.2.8 *Adverse drug reactions reporting forms containing all the relevant information*

For a PV system to operate successfully and effectively, it is vital that ADRs are reported, and thus an ADR reporting form has to exist (WHO, 2006b). The report must capture the relevant information, i.e. patient information, suspected product or drug information, and a description of the ADR; moreover, a degree of standardisation is required (WHO, 2006b). Furthermore, if relevant information is omitted or questioned, the system must be able to verify the report by contacting the necessary parties (Olivier *et al.*, 2016; Poirot *et al.*, 2016; Nguyen *et al.*, 2018).

4.2.2.9 *Collaboration between clinical trials and pharmacovigilance systems*

The WHO defines a clinical trial as any research study that evaluates the health effects by prospectively assigning humans to health-related studies (WHO, 2015c). However, in the literature it is argued that there should be collaboration between the clinical trial phase of a drug and the PV monitoring system (Zun, 2014; Harugeri, Shastri and Patel, 2017). It is thus imperative that, during the clinical trial phase, the planning and operation of the PV system is taken into account. This entails considering if additional or more strenuous PV activities would need to be included (Iwasaki, Kaneko and Narukawa, 2017). Furthermore, certain improvements are needed for the clinical trial and PV databases when addressing the timeliness, duplication, coverage and harmonization of the data collection (Harugeri, Shastri and Patel, 2017).

4.2.2.10 *Context-specific conditions*

Although a PV system requires some form of standardisation with regard to ADR reports, it is argued in the literature that context-specific conditions have to be taken into account too (Zun, 2014; Cheaib, 2016). This entails considering specific populations of patients (such as paediatric patients, pregnant patients, elderly patients, and traditional medicine users), as well as drugs or treatments for specific disease burdens (i.e. HIV, TB etc.) and specific countries when developing a PV system and/or processes (Zun, 2014).

4.2.2.11 *Proactive reporting processes*

Spontaneous reporting methods are the most common method used with regard to ADR reporting; however, from the literature it is evident that a more proactive approach needs to be taken, which entails modernising and customising the entire reporting system (Hanzl-Dujmović, Sulić-Milišić and Starešinić-Šernhorst, 2007). Furthermore, in order to reduce under-reporting, implementing either compulsory reporting or alternatively providing some form of compensation may be required (Khattri *et al.*, 2012).

4.2.3 Systematic literature review related to Medicine Patent Pool requirements

This systematic literature review was conducted to identify the possible requirements of the MPP within the context of PV systems. As was the case in the previous systematic literature reviews, Scopus and PubMed were consulted and search terms related to the context of MPP and PV were used; these are summarised in Table 4.2. The search term “MPP or Medicines Patent Pool” could not be used directly, as no relevant documents were identified with this search term. Thus, as in the systematic literature review conducted in Section 3.4.1, which searched for the challenges associated with MPP, the terms “drug manufacturing” and “drug

supply” were used instead, as the MPP contributes to the manufacturing and supply of drugs. The term “requirements” was not included during the search protocol as had been done in the previous review (see Section 4.2.1), because the inclusion of this term limited the initially identified documents to five documents. Thus, in an attempt to identify possible additional relevant documents, this term was excluded, although it was still considered when the documents themselves were closely reviewed.

By using the search terms listed in Table 4.2, a total of 74 potentially relevant documents were identified. Furthermore, to ensure that only the most relevant documents were considered, inclusion/exclusion criteria were used, which entailed only including documents that were published from 2010 onwards, as the MPP was only established in that year, and thus it would not be relevant to search from 2000 onwards, as with the previous search, as well as only including documents that were published in English. Once these criteria had been applied, it reduced the total number of articles to 37. The abstracts of these remaining documents were then reviewed, and any documents that were not specifically relevant to requirements related to PV within the context of drug manufacturing or supply (i.e., with regard to the MPP) were removed, until 18 relevant documents remained. The last step entailed reviewing the entire documents, and any documents that did not contribute to the identification of any requirements related to PV within the context of MPP or drug supply or manufacturing, were removed. In the end, a total of relevant documents remained, which were then closely reviewed.

Table 4.2: List of search terms used to identify MPP related requirements

Search base	Key words or phrases used	Initial number of documents	Number of documents after inclusion/exclusion criteria	Number of documents after abstract screening	Number of documents after final screening
Scopus	(“drug manufacturing” OR “drug supply”) AND (pharmacovigilance OR (drug safety monitoring))	54	30	12	6
PubMed	(“drug manufacturing” OR “drug supply”) AND (pharmacovigilance OR (drug safety monitoring))	27	20	6	0
Total number of documents		74	37	18	6

4.2.4 Requirements relating to Medicine Patent Pool identified from the literature

After analysing the relevant documents, a total of 4 requirements related to PV within the context of the MPP (or subsequently drug manufacturing and supply) was found. Some of these were similar in nature to those previously identified in Section 4.2.2. However, where this is the case, there are specific considerations that the MPP calls for in the development of the requirement specification for that will guide the development of a decision support tool that facilitates the development of context-specific PV systems.

4.2.4.1 *Education of pharmaceutical companies on pharmacovigilance*

As previously stated the system must incorporate PV education. In the context of the MPP, however, the PV education should be incorporated into the education of pharmaceutical companies, i.e. pharmacists and stakeholders involved during R&D of drug manufacturing

(Vashisth, Singh and Nanda, 2012; Flood *et al.*, 2017). In a study done by Flood (2017) on generic pharmaceutical companies, it was found that the pharmaceutical staff had very limited or no pharmacy-specific training, which included drug safety monitoring or PV related education (Flood *et al.*, 2017). As the MPP is associated with generic drug manufacturing companies, it is important to extend PV education into the drug manufacturing and supply environments.

4.2.4.2 Definition of stakeholders' roles with respect to pharmaceutical companies

When considering the different stakeholders involved with drug safety monitoring, it has been found that pharmaceutical companies need to be more actively involved with the PV process and reporting of ADRs (Arabia, 2015; Nwaiwu, Oyelade and Eze, 2016; Nguyen *et al.*, 2018). Thus, pharmaceutical companies' roles within the context of PV systems should be clearly defined, in order to improve quality control in the PV system (Arabia, 2015; Nwaiwu, Oyelade and Eze, 2016; Nguyen *et al.*, 2018).

4.2.4.3 Quality control for substandard or counterfeit drugs

In the context of the MPP, inadequate quality drugs, i.e. substandard or counterfeit drugs, are more prevalent, as stated in Sections 3.2.5 and 3.2.23 (Johnston and Holt, 2013). Thus, PV systems must be able to improve quality control for these kinds of drugs. PV systems are thus required to have a higher and more sensitive index with respect to inadequate quality drugs (i.e. counterfeit or substandard drugs) by having systems in place (i) when reports related to ineffective drugs are received, or (ii) when there are presenting circumstances that raise suspicions with respect to a reported drug (Khurelbat *et al.*, 2014; Beninger, 2017).

4.2.4.4 Context-specific conditions with respect to traditional medicines

According to the literature, traditional medicines raise unique issues for a PV system, for instance with regard to the occurrence of drug-herb interactions and previously unknown ADRs; a PV system within the context of these drugs must be able to address these issues effectively (Beninger, 2017). In this research inquiry, it has been found that traditional medicines are often associated with the MPP, as indicated in Section 3.2.24 and the PVCCL, and thus, when a context-specific PV system is being considered for the MPP, systems must be in place to address these unique issues related to traditional medicines.

4.2.5 Systematic literature review related to HIV, TB and Hepatitis C requirements

The focus of the third systematic literature review was to identify requirements related to HIV, TB and Hepatitis C within the context of a PV system. As was the case with the previous systematic literature review described in Section 4.3.2, the academic databases Scopus and PubMed were used as the primary search databases to conduct a similar search protocol to identify requirements related to the specific diseases, viz. HIV, TB and Hepatitis C. Table 4.3 indicates the different search terms used, similar to the previous systematic literature reviews, but now within the context of HIV, TB and Hepatitis C. However, it should be noted that, in this systematic literature review, the search term 'characteristics' was included together with 'requirements', as the initial search protocol, only using 'requirements', only identified a relatively limited number of documents (i.e., only 23 relevant documents in total). Thus, after the search was extended to include the word 'characteristics', a total of 107 relevant articles were identified.

Thereafter, to ensure that only the most relevant documents were included in this research, inclusion/exclusion criteria were used, which entailed only including documents that were published from 2010 onwards, as this was the year in which the MPP was established, as well as only including documents that were primarily written in English. After these inclusion/exclusion criteria were applied, 96 relevant documents remained; their abstracts were reviewed to identify any requirements that these specific diseases, (i) HIV, (ii) TB, and (iii) Hepatitis C, would call for in a PV or drug safety monitoring system; this reduced the number to 68 relevant documents. The final step of the systematic literature review was to review the full remaining documents and remove those documents that were not relevant to the specific PV requirements related to (i) HIV, (ii) TB, and (iii) Hepatitis C, and a total of 15 relevant documents remained. Furthermore, after additional sources, such as Google Scholar, were used, five additional documents were included as serendipitous findings. A total of 20 relevant documents were thus identified and used.

Table 4.3: List of search terms used to identify HIV, TB and Hepatitis C related requirements

Search base	Key words or phrases used	Initial number of documents	Number of documents after inclusion/exclusion criteria	Number of documents after abstract screening	Number of documents after final screening
Scopus	(HIV OR (TB OR tuberculosis) OR (Hepatitis C)) AND (requirements* OR characteristics*) AND (pharmacovigilance OR (drug safety monitoring))	121	54	26	8
PubMed	(HIV OR (TB OR tuberculosis) OR (Hepatitis C)) AND ((requirements* OR characteristics*) AND (pharmacovigilance OR (drug safety monitoring)))	73	66	42	7
Google Scholar	Serendipitous findings				5
Total number of documents		107	96	68	20

4.2.6 Requirements relating to specific diseases, HIV, TB and Hepatitis C identified from the literature

After the relevant documents identified were reviewed a total of nine requirements related to HIV, TB, and Hepatitis C were identified with respect to PV systems. It was found that many of the requirements identified are similar to those previously identified (see Section 4.2.2), however there are unique considerations pertaining to (i) HIV, (ii) TB and (iii) Hepatitis C that have to be taken into account. Thus, in the case where a similar requirement is listed, the unique aspects which require consideration within the context of these disease are addressed. A detailed overview of each of the requirements occurrences within the identified literature can be found in Appendix B.

4.2.6.1 Context-specific pharmacovigilance education

In the literature, it is argued that PV education should be country-specific as well as patient-specific, by focussing more on the highly prevalent illness that are present in the specific environment (Dube *et al.*, 2012; Dennison, Wu and Ickes, 2014; Masenyetse, Manda and

Mwambi, 2015; Leufkens *et al.*, 2016; Kigozi *et al.*, 2018). Furthermore, patients should not only be educated how to identify and report ADRs, but such education should focus on being context-specific with regard to the specific ADRs associated with the prevailing illnesses or diseases within a particular environment. According to Masenyetse, Manda and Mwambi (2015) it has been advised that incorrect beliefs and perceptions regarding treatments should also be addressed by such education (Masenyetse, Manda and Mwambi, 2015;).

4.2.6.2 More active reporting processes

According to Bailey *et al.* (2016), when considering HIV, TB and Hepatitis C, a more active approach to monitoring and ADR reporting should be adopted (Bailey *et al.*, 2016). Active reporting process are required within the context of these disease as the disease are often attributed to low treatment adherence, see Section 3.2.8, and thus in an attempt to focus on early ADR detection, active reporting processes are advised (Akshaya Srikanth *et al.*, 2012). Literature argues that in addition to spontaneous reporting, other methods and techniques such as targeted spontaneous reporting (TSR) and cohort event monitoring (CEM) should be considered for PV systems related to these diseases (Masenyetse, Manda and Mwambi, 2015; Bailey *et al.*, 2016; Leufkens *et al.*, 2016; McEwen, Vestergaard and Sanburg, 2016; Rachlis *et al.*, 2016).

In a study by Manickum and Suleman (2012) focusing on PV systems related to HIV, it was found that enforcing compulsory ADR reporting significantly reduced under-reporting within the context of HIV treatments (Manickum and Suleman, 2012). In other HIV related studies, it was also found that a lack of incentivising ADR reporting may have contributed to an increase in under-reporting. Furthermore, if no form of PV promotion and/or prioritisation is incorporated, then other tasks, such as treatment of patients, is prioritised above drug safety monitoring and ADR detection (Rachlis *et al.*, 2016).

4.2.6.3 Standardised but context-specific adverse drug reaction reports

In the literature it is argued that ADR reporting forms should be standardised, but also allow for context specificity when considering the environments where TB and HIV are prevalent (Avong *et al.*, 2015). This standardisation entails ensuring the consistent use of terminology, i.e. adverse reaction vs adverse event (Bailey *et al.*, 2016). Furthermore, when considering HIV, TB and Hepatitis C, the reports should be patient- and disease-specific (Masenyetse, Manda and Mwambi, 2015; Leufkens *et al.*, 2016).

4.2.6.4 Work organisation structure

In environments with a higher burden of disease related to (i) HIV, (ii) TB, and (iii) Hepatitis C, when addressing the processes of a PV systems, i.e. the collection, analysis, and evaluation of ADRs, there are certain factors related to 'work organisation'¹⁵ that could complicate or hinder the process, such as poor access to computers, multiple conflicting demands, and poor information technology systems design (Bailey *et al.*, 2016). Thus, when designing a PV

¹⁵ Work organisation refers to the distribution and coordination of tasks within an organisation to achieve the desired service or results.

system in these environments, it is important to consider the work organisational factors, i.e. limited access to specific resources.

4.2.6.5 Consideration of vulnerable patients

When considering HIV, TB and Hepatitis C, certain patients groups that are more susceptible to these diseases, and more attention should be placed on such vulnerable patient groups, which include (i) older patients, (ii) pregnant patients, (iii) first regime patients, and (iv) patients who take multiple different drugs (Staszewski *et al.*, 1999; Eluwa, Badru and Akpoigbe, 2012; Masenyetse, Manda and Mwambi, 2015).

A study conducted by Masenyetse (2015) that considered ADR occurrences in HIV patients receiving ART, found that patients older than 38 years had a significantly higher rate of ADR occurrence than patients younger than 30 years (Masenyetse, Manda and Mwambi, 2015). These results are also supported by other studies (Staszewski *et al.*, 1999; Eluwa, Badru and Akpoigbe, 2012). Furthermore, a study by Masenyetse (2015) also established that there is a difference in ADR occurrence based on sex, as there is a slightly higher rate of ADR occurrence in female patients compared to male patients (Staszewski *et al.*, 1999; Eluwa, Badru and Akpoigbe, 2012; Masenyetse, Manda and Mwambi, 2015). In the literature it was also found that patients starting their first regime treatments should be monitored more closely (Dube *et al.*, 2012; Masenyetse, Manda and Mwambi, 2015; Leufkens *et al.*, 2016).

4.2.6.6 Definition of stakeholders' roles

When addressing ADR reporting within the context of HIV, TB and Hepatitis C treatment projects, a designated person in charge of PV is required (Rachlis *et al.*, 2016). Furthermore, studies also affirm that reporting facilities and PV stakeholders actively need to increase their involvement in the reporting process, through prioritising funding and resources (Rachlis *et al.*, 2016).

4.2.6.7 Consideration of specialised drugs

In a study done by Giezen (2010) related to the safety profiles of biologicals, it was established that traditional medicines have a different safety profile when compared to other drugs in traditional PV databases; however, there is limited data available on the nature of ADR reporting in relation to these traditional medicines and thus more careful consideration should be paid to the ADR reporting related to these medicines (Giezen *et al.*, 2010). Furthermore, the ADRs associated with inactive ingredients and ingredients related to traditional medicines, should also be taken into account when developing a PV system in the context of HIV, TB and Hepatitis C (WHO, 2002b; Nwaiwu, Oyelade and Eze, 2016).

4.2.6.8 Implementation of quality control systems

In a PV system, it is vital that regular quality control checks are in place and conducted to ensure that all different phases and processes are up to standard (Kimutai *et al.*, 2017). Furthermore, the quality control activities are also required to verify the quality of the data as well as the consistency, accuracy and completeness of the records (Kimutai *et al.*, 2017). Addressing the improvement of quality control systems could also contribute to the early detection of sub-standard and counterfeit drugs, which are often associated with HIV and TB treatments (McEwen, Vestergaard and Sanburg, 2016).

4.2.6.9 *Incorporation of public awareness*

When addressing PV systems that are implemented in environments with a higher burden of HIV, TB and Hepatitis C, public awareness with respect to PV and ADR reporting should be enhanced (Dennison, Wu and Ickes, 2014). Furthermore, targeted interventions specifically aimed at the populations where these diseases are more prevalent, such as college students, pregnant women, and sex workers, should be implemented to improve awareness (National Institute on Drug Abuse, 2012; Dennison, Wu and Ickes, 2014). In this regard, the vulnerable patient groups, identified in Section 4.2.6.5, should also be targeted by these intervention strategies.

4.2.7 Systematic literature review related to resource limited settings requirements

As was the case in the previous three systematic literature reviews, Scopus and PubMed were consulted as primary databases to identify requirements related to RLS in the context of PV. Similar search terms and inclusion/exclusion criteria were applied to identify the most relevant documents to review and analyse when considering requirements pertaining to RLS and PV systems.

The search terms used within the context of RLS and PV systems are listed in Table 4.4. The term “requirements” was excluded during the search protocol here, although it had been used during the previous systematic literature reviews. This is because only a very limited number of documents were identified when using this search term (two documents from both databases before any criteria had been applied), as had happened during the systematic literature review related to the MPP (Section 4.2.3). Thus, in an attempt to enlarge the search protocol, and possibly identify additional relevant documents, this term was initially excluded but still considered during a revision of the documents. Using these search terms, a total of 33 relevant articles were identified; thereafter, as with the previous systematic literature reviews, two inclusion/exclusion criteria were applied to ensure that only the most relevant documents were included for review and analysis. Only documents dated from 2010 onwards were included, as the MPP was established in 2010, and only documents published in English were included. Once these criteria had been applied, a total of 16 documents were identified from Scopus and 14 from PubMed. Furthermore, as with the previous systematic reviews, if the same document was present in both sets of documents, duplicates were removed. Thereafter, the remaining documents’ abstracts were screened to identify requirements in the context of PV systems related to RLS. A total 23 relevant documents were identified in this way. The final phase of the review was to evaluate the entire document, and 4 documents were found to be relevant. In addition, Google Scholar was consulted for serendipitous findings, and a total of eight additional documents were included.

Table 4.4: List of search terms used to identify RLS related requirements

Search base	Key words or phrases used	Initial number of documents	Number of documents after inclusion/exclusion criteria	Number of documents after abstract screening	Number of documents after final screening
Scopus	“resource limited settings” AND (pharmacovigilance OR “drug safety monitoring”)	18	16	11	4
PubMed	“resource limited settings” AND (pharmacovigilance OR “drug safety monitoring”)	15	14	12	0
Google Scholar	Serendipitous findings				8
Total number of documents		33	30		12

4.2.8 Requirements relating to resource limited settings identified from the literature

The 12 documents identified during the systematic document identification and selection process, as outlined above, were reviewed and a total of nine requirements related to RLS within the context of PV systems were identified; they are discussed in the following sections. As with the requirements relating to HIV, TB, and Hepatitis C, it was found that a number of these requirements were similar in nature to those identified in Section 4.2.2 relating to traditional PV systems. However, as stated previously with respect to the requirements relating to the MPP and (i) HIV, (ii) TB and (iii) Hepatitis C, where similar requirements were identified, their unique consideration in respect of RLS is highlighted.

In Appendix B, a detailed overview is given of the occurrence of each of the requirements found in the identified literature.

4.2.8.1 Addressing pharmacovigilance education and capacity building in academia

In the context of RLS, it has been found that, in the academic fields related to healthcare, i.e., in universities’ HCP curriculum, there is a lack of PV education (Olsson, Pal and Dodoo, 2015b). Limited courses related to PV are offered in RLS, and there is a need to not only include PV subjects in undergraduate programs but also to encourage their development in postgraduate fields, such as PhDs related to PV (Andreatta *et al.*, 2014; Hagemann *et al.*, 2014; Olsson, Pal and Dodoo, 2015a). Furthermore, it has been found that addressing capacity building in RLS, through education interventions, may improve oversight of ADR detection and medical management related to drug safety monitoring (Godfrey *et al.*, 2014).

4.2.8.2 Adoption of additional reporting and more active reporting processes

For a PV system to function effectively in the context of RLS, both active and passive surveillance methods are required (Mehta, Dheda, Steel, M Blockman, *et al.*, 2014). Spontaneous reporting programmes in RLS have been found to provide little support for addressing all the needs of health systems, resulting in low reporting rates, which subsequently lead to inadequate credible risk profiles being developed (Olsson, Pal and Dodoo, 2015b). Thus, additional methods are needed to improve safety profiling (WHO, 2012; Olsson, Pal and Dodoo, 2015a).

4.2.8.3 Collaboration with clinical trials

PV systems within the context of RLS require strong collaboration between clinical trials and PV systems (Godfrey *et al.*, 2014). Randomized clinical trials in combination with long-term follow-up of trial participants can be seen as a great source for ADR reporting. Such a collaboration with clinical trial databases can allow for comparisons to be drawn between different drugs, toxicity assessments, and the evolution of drug resistance (Godfrey *et al.*, 2014). One such study that considered the collaboration between these databases was the *Development of AntiRetroviral Therapy in Africa Trial* (Miller, Nwokike and Stergachis, 2012). Furthermore, Godfrey *et al.* (2014) states that clinical trial oversight (i.e. monitoring of the patients partaking in the clinical trial, and the data gathered), which is an essential aspect to ensure the integrity of the data and the protection of the research participants, is a challenge faced in many RLS and thus quality management approaches need to be incorporated to support the integrity of the data quality and protect participants (Godfrey *et al.*, 2014; Stenning *et al.*, 2018).

4.2.8.4 Adoption of effective communication and feedback channels

PV systems are safety monitoring systems that provide information related to the observation of ADRs, the reporting and evaluation of ADRs, and the mediation thereof, to ensure the safety of patients (Olsson, Pal and Dodoo, 2015a). Thus, communication and feedback systems should be incorporated within PV systems to ensure that patients and other stakeholders, including HCP, regulatory bodies and pharmaceutical companies, are informed about actions related to ADRs (Olsson, Pal and Dodoo, 2015a). However, in RLS it is often more challenging to provide stakeholders effectively with the necessary information and thus PV systems in the context of RLS must adopt effective communication and feedback systems (Mehta, Dheda, Steel, M Blockman, *et al.*, 2014; Olsson, Pal and Dodoo, 2015a).

4.2.8.5 Adoption of patient involvement during the reporting stage

PV systems in RLS require communication channels to exist, not only between HCP, regulatory authorities, and PV centres but also between these stakeholders and patients (Olsson, Pal and Dodoo, 2015a). However, in the literature it is argued that the involvement of patients with respect to PV in RLS should extend past the action of communication and should include the reporting of ADRs too. In the modern-day landscape, the growing usage of technologies has fundamentally changed the methods of reporting ADRs and thus it is necessary to incorporate patient self-reporting in order to address the under-reporting of ADRs in RLS (Olsson, Pal and Dodoo, 2015a).

4.2.8.6 Existence of a context-specific pharmacovigilance system

In RLS, there is a need for a context-specific PV system, with the long-term goal of developing country- and context-specific PV systems within these RLS environments (Atuah, Doodoo and Winstanley, 2007; Caudron *et al.*, 2008; Miller, Nwokike and Stergachis, 2012; Mehta, Allen, *et al.*, 2014). Countries should identify the objectives that would address the PV needs of the particular environment in which the system will have to function (Mehta, Allen, *et al.*, 2014). Furthermore, it is argued in the literature that, when considering the development of a PV system within the context of RLS, the following aspects should be taken into consideration: (i) the characteristics of the target patients, (ii) the drug treatment(s) that are being monitored,

(iii) the impact of these diseases within the specific context, and (iv) the conditions of the environment in which the PV system would have to be implemented (Mehta, Allen, *et al.*, 2014).

4.2.8.7 Reporting processes in resource limited settings

In RLS, certain requirements have to be taken into account when considering the process of reporting. As the HCP to patient ratio is low in RLS, the time allowed for recording and capturing ADRs is often limited (Olsson, Pal and Dodoo, 2015a). Innovative, non-time-consuming methods of data capturing must thus be explored and adopted (Olsson, Pal and Dodoo, 2015a). Furthermore, having limited resources available means that the ADR reporting forms within these environments must be transparent, uncomplicated and not time-consuming to administer or complete (Atuah, Doodoo and Winstanley, 2007; Olsson, Pal and Dodoo, 2015a; Ha *et al.*, 2016). The use of standard terminology is also important to improve the uniformity of data collection and monitoring (WHO, 2012). In RLS, standard operating procedures are necessary in order to assist and improve the review capacity of the health system (WHO, 2012; Godfrey *et al.*, 2014; Poirot *et al.*, 2016). The reports must also be available in the local languages of the relevant countries or regions (Olsson, Pal and Dodoo, 2015a).

4.2.8.8 Remuneration for the reporting of adverse drug reactions

RLS are often associated with under-reporting of ADRs, and thus incentives and remuneration should be included to improve reporting in these environments and subsequently improve patient relations. These incentives should be directly related to the performance of the HCP with regard to PV and ADR reporting (Olsson, Pal and Dodoo, 2015a).

4.2.8.9 Adoption of national strategy with respect to pharmacovigilance

The countries associated with RLS need to establish national strategies that define the realistic objectives related to PV requirements within the context of the specific country (Mehta, Allen, *et al.*, 2014). Having national engagement and a national strategy for a PV system would create a sense of shared responsibility and ownership of a PV program. These strategies should include stakeholders, such as practicing clinicians, nurses, doctors, academics, policy-makers, pharmaceutical companies and government agencies/regulatory bodies (Mehta, Allen, *et al.*, 2014).

4.3 CONSULTING THE PHARMACEUTICAL VALUE CHAIN CHALLENGES LANDSCAPE

In order to ensure that a proposed a decision support tool that facilitates the development of context-specific PV systems allows for the required contextual specificity relating to the MPP drug provision systems and the four niche factors, the unique set of challenges posed by these factors, as identified in Chapter 2 and Chapter 3, have to be taken into consideration.

Thus, in order to determine whether the identified requirements are adequate in addressing these challenges, a relationship matrix is developed, which indicates which of the identified challenges, as depicted in the PVCCL, are addressed. Furthermore, this relationship matrix also indicates whether additional requirements should be considered.

In this section, the relationship matrix as well as the additional requirements posed by the challenges that have not been addressed are discussed.

4.3.1 Relationship diagram of requirements and pharmaceutical value chain challenges landscape

The requirements identified during the systematic literature review are mapped against the different challenges in a relationship matrix, to determine if there are possible additional requirements to consider. This relationship matrix is illustrated in Figure 4.2. If a requirement was found to address a challenge, this is indicated using a “X”. If none of the identified requirements address a specific challenge, an additional requirement pertaining to the specific challenges is developed and will be discussed in the following section.

Requirements identified from systematic literature reviews																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																
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Figure 4.2: Matrix pertaining to identified requirements and the PVCCL

4.3.2 Additional requirements identified

The relationship diagram was used to identify possible additional requirements, as the following challenges were not addressed: (i) diagnostics, (ii) laboratories, and (iii) labelling.

Thus, two additional requirement specifications were developed, one pertaining to diagnostics, and laboratories (as these two challenges are part of the same challenges group see PVCCL) and one with reference to the challenges related to labelling. Furthermore, as these three challenges are considered within the environment of the MPP and thus associated with the niche factor of MPP (see Section 3.4), it was decided to include these two requirements in this discussion of the MPP related requirements.

MPP 5: Clear lines of communication have to exist between PV stakeholders, pharmaceutical companies, and diagnostic labs.

When considering the PVCCL, one of the identified challenges was that there is a lack of communication between diagnostic testing facilities, laboratories and PV stakeholders, such as HCP, regulatory bodies and PV centres. This lack of communication extends further to pharmaceutical companies. Thus, it is required that a context-specific PV system has clear communication channels between PV stakeholders and diagnostic testing facilities or laboratories, as well as with pharmaceutical companies.

MPP 6: Drug labels must be clear, readable and unambiguous, especially the section on adverse drug reactions.

To overcome the challenge posed by drug labels within the context of inadequate quality, the a context-specific PV system should ensure that drug labels contain all the pertinent information related to ADRs as well as information related to the pharmaceutical companies and to the manufacturing details. Furthermore, there must be systems in place if deficient or faulty drug labels are found.

These two additional requirements, as well as the requirements identified during the systematic literature were synthesised to develop a preliminary requirement specification, which will be discussed in more detail in the following section.

4.4 PRELIMINARY REQUIREMENT SPECIFICATION

From consulting the literature and the PVCCL, a preliminary requirement specification was developed that considers the 4 niche factors, namely, (i) traditional PV systems (ii) MPP, (iii) HIV, TB and Hepatitis C and (iv) RLS. The preliminary requirement specification has a specific set of requirements related to each of the said niche factors, and it is found in Appendix C. However, to authenticate the developed requirement specification a verification process was conducted, which entailed consulting SMEs from different fields relevant to this research inquiry. This approach and the results will be discussed in more detail in the following section.

4.5 VERIFICATION OF REQUIREMENT SPECIFICATION

During the requirement analysis approach, the PVCCL and the literature were consulted to develop a preliminary requirement specification, for the context of MPP drug provision

systems that considers the four niche factors. To confirm the credibility and reliability of this developed set of requirement specifications, and to identify possible inconsistencies or shortcomings, a verification process was conducted with SME.

The verification process was conducted by using a questionnaire, with SMEs from various backgrounds within the context of pharmaceutical industry and PV. Four separate verification processes were conducted, pertaining to each of the specific niche factors. These processes were similar in nature, but the objective of each specific process was to verify the credibility of the requirements related to the specific factor under consideration. Each verification process consisted of (i) a pre-read document, providing a brief overview of the background of the research and a breakdown of the requirements related to the specific niche factor, and (ii) a corresponding questionnaire. The questionnaire focused on determining the relevance of the specific niche factors' identified requirements with regard to the development of a PV system. Using a seven-point Likert scale, the SMEs were requested to rate each of the identified requirements and to make additional comments pertaining to the provided rating. Furthermore, they were also given the opportunity to include additional requirements if they believed there were gaps in the proposed requirement specification. SMEs from different fields within the healthcare landscape, i.e. the pharmaceutical industry, PV and academia, were consulted. Each SME was requested to complete the verification of the niche factor related to their specific field of expertise. They were granted an opportunity to complete the other verifications, if their expertise expanded across those fields. The pre-read documents and questionnaires used during this verification process can be found in Appendix D.

Eight SMEs participated in the verification process; an overview of their qualifications and experience can be found in Table 4.5 along with an indication which of the four verifications they completed.

Table 4.5: Overview of SME background experience and qualifications

SME number	Degree/Qualification	Background experiences	Niche Factor Validation
1	BEng (Industrial) MEng (Industrial)	Advisory associate at PricewaterhouseCoopers (PwC), a multinational professional services network, from 2018 to the present. Master's thesis focussed on a topic within pharmacovigilance (Investigated challenges of PV in SSA and how existing technologies can be leveraged to address these challenges).	Traditional PV systems
2	MPharm DPhil in Clinical Medicine	PhD student at the University of Oxford. Thesis topic within the field of pharmacovigilance. Coordinator of Global Pharmacovigilance open-access collaboration.	Traditional PV systems,
3	MB, BS in Medicine	Board member and treasurer of ISoP (International Society of Pharmacovigilance) (2016 to the present) Principal consultant at the NDA Group AB, a drug development consultancy company (2007 to the present) The deputy qualified person of PV at Johnson & Johnson (2005 – 2007). The Senior Medical Assessor of the Medical and Healthcare products Regulatory Agency of the United Kingdom (1994 – 1999).	Traditional PV systems

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SME number	Degree/Qualification	Background experiences	Niche Factor Validation
4	MBChB MBA	CEO and co-finder of VICORE HEALTH, a medical and regulatory affairs partner in Africa (2018 to the present). Founder of EMHC, an African healthcare and pharmaceutical consultancy. Area medical director at GlaxoSmithKline (GSK), a leading international pharmaceutical company (2015 – 2018). Medical advisor (2010 – 2012) and business director (2012 – 2013) at Pfizer, a leading international pharmaceutical company.	Traditional PV systems
5	BSc (Hons) MPH Epidemiology PhD Clinical Pharmacology	Head of clinical research at University of Cape Town (UCT) (2002 to the present). Clinical operations manager at i3 Research, a global pharmaceutical services company (1998 – 2002). Clinical research Associate at Novo Nordisk, a global healthcare company focused on treatments related to chronic diabetes. (1996 – 1998). Coordinator of Global Pharmacovigilance open-access collaboration.	Disease burden, RLS
6	BSc Molecular Biology and Biotechnology PhD Eng. candidate (Industrial)	PhD research in Pharmacovigilance at the University of Stellenbosch (2017 to the present). Part-time consultant at Nova Economics, management consulting company.	Disease burden, RLS
7	BSc in Biochemistry	Deputy Qualified Person for Pharmacovigilance at Salom Pharmacy Ltd Ghana (2017 to the present). Lab officer at Wenchi health centre, a healthcare facility in Ghana (2014 – 2015).	Traditional PV systems, Disease burden, RLS, MPP
8	Bachelor's degree in applied biology Master of Science in Clinical Trials program PhD Candidate	PhD research in Pharmacovigilance at the University of Sheffield, School of Health and Related Research (2014 to the present). Member of ISOP Member of the Clinical Human Factor Group, a charity aimed at improving the healthcare environment. Member of the Pharmaceutical Information and Pharmacovigilance Association. Member of Pharmaceutical and Human Factor Group, an organisation focused on the systems within a pharmaceutical industry.	RLS

4.5.1 Verification results

After the verification processes related to each of the niche factors were completed, the results were analysed and evaluated. These results are graphically represented in Figure 4.3, indicating how each of the different SME rated the specific requirement with reference to the Likert scale. It can be seen that the majority of the SMEs were in agreement that the identified requirements, related to each of the niche factors, were mandatory for the development of a PV system within the context of this dissertation, i.e., MPP drug provision systems.

However, as can be seen too, there were certain requirements where the SMEs were in disagreement, and a more detailed description of the results pertaining to these requirements (PV7, PV8, PV9, PV10, PV11, RLS8) is provided in the following subsection.

Furthermore, they were also consulted with respect to the absence of any requirements related to the niche factors within the context of drug safety monitoring or PV. However, no additional requirements were identified to be include, as the SMEs were satisfied with the identified requirements.

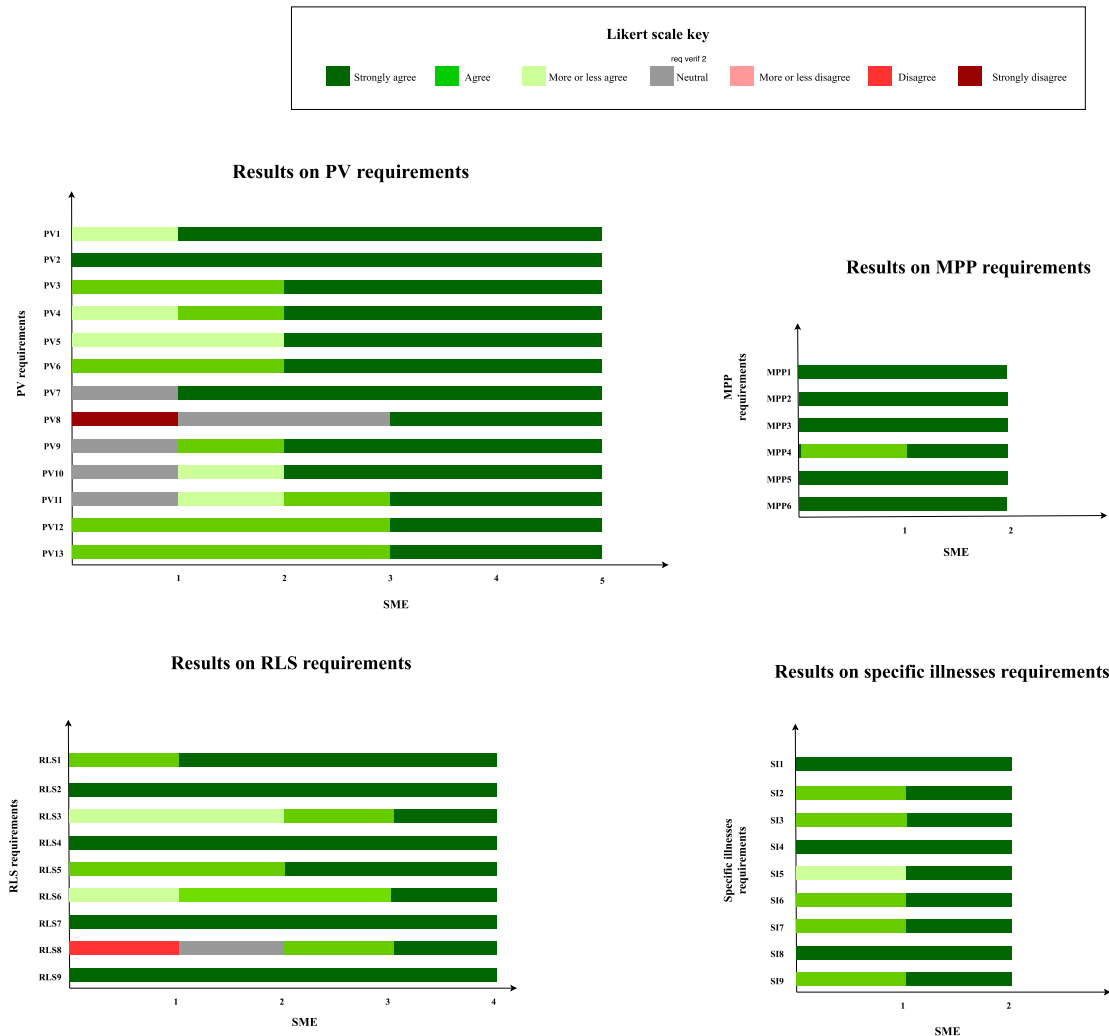


Figure 4.3: Results of requirement specification verification

4.5.2 Areas for improvement

As previously mentioned, the results showed that there were six requirements where the different SMEs differed with regard to their contribution to the development of developing a decision support tool that facilitates the development of context-specific PV systems. Thus, in order to get a better understanding of this feedback, these six requirements are discussed in detail below. Each of the requirements in question is provided below, along with the SMEs' comments pertaining to the requirement in question. The recommendations made by them were taken into consideration and the necessary adjustment, if applicable, were made. These adjustments are also discussed in this section.

PV 7: The stakeholders' roles need to be clearly defined

As shown in Figure 4.4, 80% of the SMEs' strongly agreed that PV7 should be included in the requirement specification, although 20% of the SME's had a neutral view. To gain a better understanding of this rating, the SMEs' comments are summarised in Table 4.6.

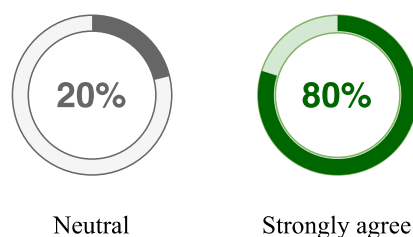


Figure 4.4: SME responses with regard to PV7

Table 4.6: SME comments with regard to PV7

SME ID no	SME rating	SME quoted commentary
4	4	Clear roles exist. Pharma resources PV extremely well based on my experience. Government departments in resource limited settings do not. Some countries in SSA have only 1 person working in government to oversee PV for the whole country's population.
1	7	As simple as this might sound, several stakeholders who participate (or who are supposed to) in PV are not entirely aware/sure what their role/responsibilities are. In this case, PV is not advocated sufficiently, and as a result is "losing" efficiency and effectiveness. However, the current problem is that many healthcare professionals are not supporting PV (even if they are instructed to) because their priorities lie elsewhere (e.g. attending to patients). It is necessary for a type of "balancing-act" to balance their current responsibilities and that of PV.
2	7	-
3	7	Accountability (legal) and responsibility needs to be defined through a hierarchical analysis to demonstrate who is legally culpable and where control lies.
7	7	-

From the results, it is clear that defining the roles and responsibilities of the different stakeholders involved with PV is a valid requirement to ensure the effectiveness of a PV system. However, it was highlighted by SME 4 that there is a clear difference between the responsibility and accountability aspects of the different stakeholders' and that this needs to be incorporated into the system.

PV8: ADR reporting forms need to contain all relevant information

With regard to PV8, there was disagreement between the SMEs on the inclusion of this requirement. As depicted in Figure 4.5, 20% of the SMEs strongly disagreed, while 40% had a neutral perspective. As with the previous requirement, PV7, their comments are summarised (see Table 4.7).

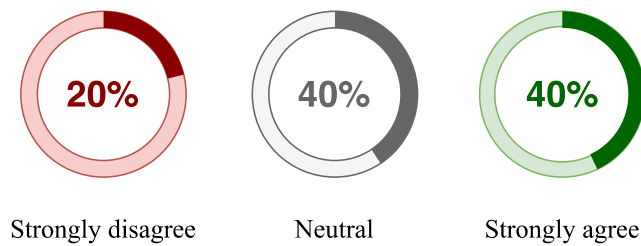


Figure 4.5: SME responses with regard to PV8

Table 4.7: SME comments with regard to PV8

SME ID no	SME rating	SME quoted commentary
1	1	No one wants to fill in a long, highly detailed form that contains several pages. Especially healthcare professionals who are already under pressure to attend to crowds of patients. Rather include minimal information in these reports, and follow up where necessary (e.g. when a definitive signal is identified).
3	4	ADR forms need to be designed with the reporter in mind. Forms need to be designed to encourage collection of all relevant information
4	4	Balance between getting people to report vs collecting all possible data fields needs to be considered. Some adverse events ask for 12 - 15 pages worth of data inputs. Not realistic that busy HCPs will provide this.
7	7	-
2	7	-

After analysing the feedback received from the SMEs with respect to requirement PV8, it can be concluded that the ADR report would need to contain the necessary information, i.e. patient information, the suspected drug and ADR, but not to request or insist that detailed, irrelevant information be captured, as time consuming, tedious documents may contribute to the already high burden of HCP, especially in RLS. Furthermore, the report should be specifically designed to bear in mind the audience and the context, i.e. vulnerable patients, specific disease burden etc. Thus, the wording of PV8 should be adapted to state that the ADR report should only require the necessary information to be captured, as stated above, and it should be designed by keeping the target audience and environment in mind.

PV9: Collaborations needs to exist between pharmacovigilance systems and clinical trials

As indicated in Figure 4.6, 20% of the SME's were either in neutral agreement or more or less in agreement with the inclusion of PV10 in a requirement specification for developing a decision support tool that facilitates the development of context-specific PV system. Thus, as with the previous requirements, the comments of the SMEs were analysed to gain a better understanding for this rating. These direct comments are provided in Table 4.8.

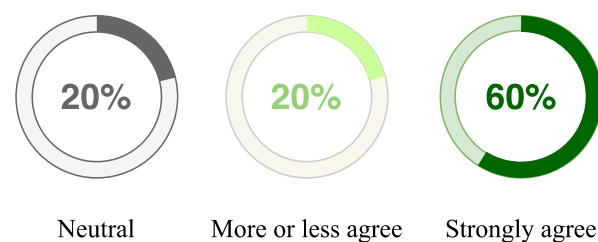


Figure 4.6: SME responses with regard to PV10

Table 4.8: SME comments with regard to PV10

SME ID no	SME rating	SME quoted comment
4	4	I would argue a link already exists. New medicines with safety signals in clinical trials (before these medicines are authorised for use) generally require additional safety studies and surveillance in countries once the drug is registered. New malaria vaccine (RTSS GlaxoSmithKline) very good example of this.
1	5	It is important for PV systems to interact with clinical trials since this is the time when new ADRs will be experienced. However, this link is difficult to achieve since the clinical trial market is so heavily governed and monopolised by pharma. Since there are several stakeholders who want "a piece of the pie" in clinical trials, PV systems will struggle to have a foothold.
2	7	-
3	7	This is a legal requirement but also has to adapt to Good Clinical Practice
7	7	-

From the results obtained regarding requirement PV10, it seems that this is a valid requirement to include, as it builds on GVP (European Medicines Agency, 2017). SME4 stated that the links between the clinical trials and PV systems do already exist, although this does not diminish the fact that this should not be a requirement for an effective PV system within the context of this dissertation.

PV10: The system must be designed for context-specific conditions

With respect to PV10, it was found that the majority of the SMEs were in agreement with this requirement to some extent (20% more or less agreed, 20% agreed, and 40% strongly agreed); 20% of the SMEs had a neutral perspective with regard to PV11 (see Figure 4.7). To gain an understanding of the ratings with respect to PV11, the commentary made by the SMEs were advised and is provided in Table 4.9.

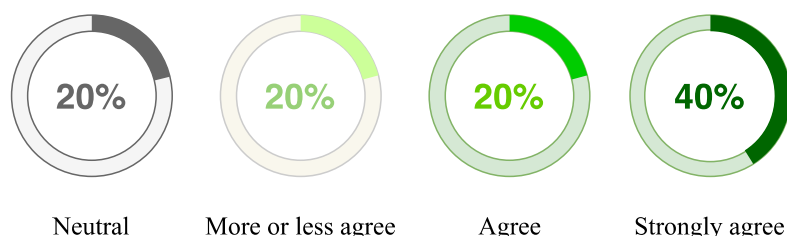


Figure 4.7: SME responses with regard to PV11

Table 4.9: SME comments with regard to PV11

SME ID no	SME rating	SME quoted comment
4	4	Whilst this is a pragmatic approach, one needs to guard against lack of standardisation. I would argue one should rather push for better resourcing to get all national systems harmonised. This will align better to most manufacturers that operate on a global level.
1	5	In several contexts, a niche PV system would be beneficial and the "answer to all the problems". However, building niche systems is very resource intensive, and one cannot build several niche systems in different settings. This will make the sharing of information and the interaction with other parties extremely difficult. Also, since PV is not necessarily a priority in several countries, it will be difficult to convince those countries to invest more resources in building a new/niche PV system.

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3	6	Overlap with PV 9
2	7	-
7	7	-

Although the SMEs do agree that developing a system that is fit for a specific environment, develop a niche system, could be beneficial, the focus should still be on developing a standardised national system. Furthermore, from the results it was also concluded that requirements PV9 and PV11 correspond and should possibly be combined.

RLS8: Reporting should be made compulsory or some form of remuneration should be granted to healthcare workers when they report adverse drug reactions

When considering the requirement, RLS8, it is found that the SMEs disagreed with this requirement. As shown in Figure 4.8, 25% of the SME's disagreed with the requirement or had a neutral perspective of the requirement, however 25% also agree, and 25% strongly agree. As with the previous requirements listed above, to gain an understanding of these ratings, the SME commentary was advised and is provided in Table 4.10.

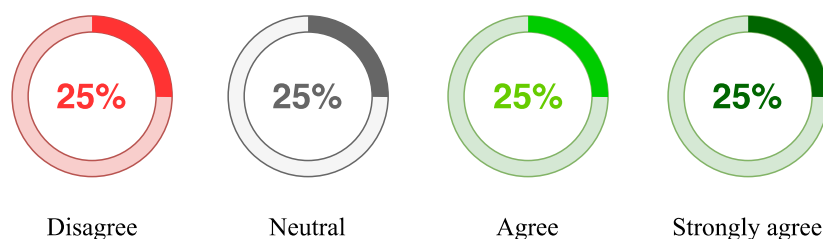


Figure 4.8: SMEs' responses with regard to RLS8

Table 4.10: SME comments with regard to RLS8

SME ID no	SME rating	SME quoted comment
8	2	The quality of reports would be reduced. Compulsion in RLS would also increase fear of blame because of medication error and possible litigation consequence. In addition, it would be a challenge to determine how much each report should be paid for. A system of reward is however important for reporting. This would improve the feedback loop.
5	4	This could be challenging to sustain and also may influence reports, so would need to be carefully investigated before implementation.
6	6	I agree that reporting should be made compulsory, however, I do not think that healthcare workers should be remunerated for reporting, it should be part of their professional responsibility.
7	7	When monetary remuneration is given for reporting ADRs, the system may be flooded with false reports because people want to make some quick money. Reporting must be made compulsory. Reporters should be recognized and given non-monetary rewards.

The findings here suggest that, although compulsory reporting in RLS could contribute do additional challenges, such as increasing fear of blame, reporting of ADRs should still be made compulsory and be seen as part of HCP's professional responsibility. However, the suggestion of using monetary remuneration should be reconsidered. Remuneration can be an effective implementation to consider, but only once it has been properly investigated and is regulated.

4.5.3 Adjustments made to preliminary requirement specification

After analysing the results of the requirement validation, adjustments were made to the preliminary requirement specifications. From the original 39 identified requirements, 8 requirements were adjusted. A description of these adjustments, each of which is related to a specific requirement, is provided below:

PV1 (PV education should form an integral part of the system) was adapted to include the aspect of educating on the *importance* of PV, as it was brought to our attention that, in order to create a culture of PV, the emphasis should be placed on providing an *understanding* of PV and not only on providing education related to the *process* of PV.

PV5 (A PV centre with an effective and functioning reporting system needs to exist) was adapted to include that the HCP and public should be made aware of existing PV centres. This is because HCP are often just not aware of PV centres in their surroundings, which contributes to a lack of reporting.

PV8 (ADR reporting forms need to contain all relevant information) was changed from having *all* the information captured to only capturing the necessary information. It was also changed to include that the report needs to be designed for the context of the specific audience group. From the verification process, it emerged that requiring the capturing of all information could be a tedious process that would place a further burden on the system. Thus, only the necessary information should be captured, such as the patient's personal information, the details of the suspected drug and the ADR.

PV11 (The system must be designed for niche specific conditions). From the verification results, it emerged that developing a niche system could be resource intensive and thus lead to more challenges within an RLS environment. It was therefore decided that the system should rather be required to be agile enough to adapt to different environment settings.

MPP5 (The stakeholders' roles need to be clearly defined) was adapted to include that patients' roles *and responsibilities* need to be communicated to them.

RLS5 (Adoption of patient involvement during the reporting stage) was adapted to include that the system should have supporting structures in place, such as a patient PV education and feedback system, in order to facilitate and incorporate ADR reporting by patients.

RLS6 (The system needs to be region specific and take the specific environments' needs into account) was changed from requiring the system to be region/niche specific to rather being agile enough to adapt to the different environments. From the validation it was gathered that, as stated above in PV9, having a specifically designed system would be more resource intensive and thus contradict having the system be able to function effectively within an RLS.

RLS8 (Reporting should be made compulsory or some form of remuneration should be granted to healthcare workers when they report adverse drug reactions) was changed from having the system incorporate remuneration to requiring the system to make ADR reporting compulsory. The system should require reporting to form part of the HCP corporate responsibility and consider non-monetary forms of compensation.

4.6 FINAL SYSTEM REQUIREMENT SPECIFICATION

The aim of this research inquiry is to consider the development of a decision support tool that facilitates the development of context-specific PV systems.

During this chapter, a three-fold requirement analysis approach was executed to identify the unique requirements called for by each of these niche factors in an effective PV system, considering the context of the challenges associated with these factors.

Taking into consideration the findings of this approach, it can be argued that (i) the minimum set of requirements for an effective PV system (WHO and The Global Fund, 2010) and the requirements associated with traditional PV systems, Section 4.2.2, are not adequate in addressing the needs of the MPP drug provision systems, and (ii) the niche factors and challenges associated with these factors require unique considerations to be taken into account when developing a PV systems within this context. It can thus be affirmed that a context-specific PV system is required when considering the niche factors within the MPP drug provision system.

Thus, in order to assist with the development of a decision support tool that facilitates the development of context-specific PV systems a requirement specification was developed that will guide the developmeny the envisage tool, using the insights gained from the systematic literature reviews, the PVCCL, and the verification process. The findings from these approaches were synthesised to develop the requirement specification, provided in Table 4.11.

This requirement specification should be considered in its entirety but specifies the requirements each of the niche factors call for within a context-specific PV system. The requirements are listed as: (i) traditional PV systems (Requirements PV1 – PV11), the MPP (Requirements MPP1 – MPP6), RLS (Requirement RLS1 – RLS9) and MPP disease burden, HIV, TB and Hepatitis C (D1 – D9). The requirement specification that guides the development of a decision support tool for which facilitates the devopmentant of a context-specific PV system is summarised in Table 4.11 – Table 4.14. Certain requirements have additional information to provide clarity.

Table 4.11: Requirement specification related to PV systems

PV related requirements
PV1: Pharmacovigilance education should form an integral part of the system.
<ul style="list-style-type: none"> • Pharmacovigilance education needs to be incorporated into the health care system at undergraduate and graduate levels of teaching. • Qualified personnel have to be in charge of pharmacovigilance within the different sectors. • The importance of PV should also be communicated to the different stakeholders to create a culture of PV.
PV2: Channels of communication have to exist between the different stakeholders involved within the healthcare system.
<ul style="list-style-type: none"> • Transparency needs to be executed between the different communication channels. • Feedback systems need to be in place between the different stakeholders.
PV3: Patient and public involvement should be adopted within the system.
PV 4: The system requires an effective database for the collecting and managing of reports.

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PV5: A PV centre with an effective and functioning reporting system needs to exist.
<ul style="list-style-type: none"> • A reporting system with adverse drug reaction reporting forms needs to exist. • The pharmacovigilance plan should take into account risk identification during product development and risk management. • A national pharmacovigilance centre needs to exist with designated staff, roles and well-defined structures. • A pharmacovigilance advisory committee needs to exist and assist on technical matters. • The HCP and the public need to be made aware of the different PV centres that exist within their areas.
PV6: The system requires effective quality management and quality control systems.
<ul style="list-style-type: none"> • Regular audits and inspections of pharmaceutical companies by healthcare workers need to be implemented. • Quality management and control systems need to be implemented.
PV7: Stakeholders' roles should be clearly defined.
<ul style="list-style-type: none"> • All organizations involved with PV need to embrace the concept of quality control and behave in a collaborative, transparent proactive way. • The difference between the stakeholders' responsibilities and their accountability needs to be defined.
PV8: ADR forms need to capture the necessary required information and should be context-specific to the audience group.
<ul style="list-style-type: none"> • Reports need to capture the minimal required information (patient contact details, ADRs experienced and suspected drug used). The report should not be tedious and long. • The report needs to be designed by keeping the reporter in mind, and their knowledge and environment.
PV9: Collaboration between pharmacovigilance systems and clinical trials has to be adopted.
<ul style="list-style-type: none"> • In clinical trials, improvements in the mode of safety data collection, timelines, duplication, harmonization, and coverage need to be explored.
PV10: The system needs to be agile and adapt to the specific environments.
<ul style="list-style-type: none"> • Specific populations/patients need to be considered when setting up a pharmacovigilance system. • It is necessary for traditional medicines to be incorporated into national pharmacovigilance programmes. • Generic drugs must be treated as a new released drug and to follow all the necessary safety reporting requirements. • Special attention needs to be placed on drugs that are suspected for defects.
PV11: A more proactive reporting process is required.
<ul style="list-style-type: none"> • A more proactive approach needs to be taken with regard to reporting. • Low-cost reporting solutions at international standards are required. • ADR reporting must be compulsory for healthcare professionals.

Table 4.12: Requirement specification related to MPP

MPP related requirements
MPP1: Pharmacovigilance education should entail educating pharmaceutical companies.
<ul style="list-style-type: none"> • PV Education should include education on specialised drugs (such as traditional medicines). • Drug manufacturing companies should be informed and educated on the importance of PV.
MPP2: Stakeholders' roles need to be defined with respect to pharmaceutical companies.
<ul style="list-style-type: none"> • Healthcare workers must be able to identify an illness and/or ADRs and report them as soon as possible. • Pharmaceutical companies need to play a vital role in the system.
MPP3: The system should address quality control for substandard or counterfeit drugs.
<ul style="list-style-type: none"> • Special attention needs to be paid to quality control monitoring of counterfeit and sub-standard drugs. • Special attention needs to be paid to quality control monitoring of specialised drugs, such as traditional medicine and paediatrics drugs. • Proper quality control should be exercised over ingredients used in traditional medicines.

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MPP4: Context-specific conditions need to be taken into account with respect to traditional medicines.
<ul style="list-style-type: none"> • Special attention needs to be paid to quality control monitoring of specialised drugs such as traditional medicine and paediatrics drugs. • Generic drugs must be treated as new released drug and to follow all the necessary safety reporting requirements.
MPP5: Communication channels should include/extend to the inclusion of pharmaceutical companies and diagnostic/laboratories.
<ul style="list-style-type: none"> • Communication channels should exist between quality control labs and PV centres. • Communication channels should exist between drug manufacturers and PV centres.
MPP6: Drug labels must be clear, readable and unambiguous, especially the section on adverse drug reactions.
<ul style="list-style-type: none"> • The labels of drug medications, especially the section on ADRs, must be easily visible. • Patients and health care professionals must easily be able to identify this section.

Table 4.13: Requirement specification related to HIV, TB and Hepatitis C

HIV, TB and Hepatitis C related requirements
D1: PV education should be context specific.
<ul style="list-style-type: none"> • PV education should be targeted at specific groups of people. Patients should be educated about their specific ADRs. • In order to improve adherence to treatment (e.g. HIV treatment) basic education and counselling should be provided.
D2: More active monitoring systems and additional methods and techniques have to be incorporated.
D3: Reports need to be standardised but also be context-specific to the investigated diseases and patient group.
<ul style="list-style-type: none"> • Reports need to be patient and illness (treatment) specific. • Standardised ADR reporting should be used. Terms/words in reports should be consistent, e.g. adverse reaction vs adverse event.
D4: Work organisation structure should be taken into consideration.
<ul style="list-style-type: none"> • The system should take the environment into account (e.g. lack of computers, internet etc.) • Reports need to be patient and illness (treatment) specific.
D5: More care needs to be taken with vulnerable patients.
<ul style="list-style-type: none"> • Special care should be taken for specific patients, such as patients who are on a first line regime. • More care should be taken when considering ADR reporting of older patients. • Patients who are on their first line of treatment should be monitored (to ensure that they do not stop the treatment).
D6: Stakeholders' roles and responsibilities need to be clearly defined.
<ul style="list-style-type: none"> • Patients should be treated professionally but compassionately (e.g., no discrimination against patients with certain illnesses). • There should be a designated person in charge of PV activities.
D7: The system should consider specialised drugs, such as traditional medicines.
<ul style="list-style-type: none"> • The specific drugs and treatments need to be listed on PV databases. • Special care should be taken with regard to traditional monitoring.
D8: The system requires proper quality management and control systems to be in place.
<ul style="list-style-type: none"> • Regular quality control checks to be performed. • The system should focus on reporting on the quality of drugs, especially on reporting suspected counterfeit and sub-standard drugs.
D9: Public awareness should form an integral part of the system and should be targeted at specific patient populations.
<ul style="list-style-type: none"> • Targeted interventions should be aimed at vulnerable patient groups and context-specific audience groups. • Community involvement should form an integral part of the system.

Table 4.14: Requirement specification related to RLS

RLS related requirements
RLS1: PV education and capacity building need to be addressed in academia.
<ul style="list-style-type: none"> • Pharmacovigilance education should be implemented in academia. This entails the inclusion of pharmacovigilance subjects into undergraduate programmes. • Capacity building should be integrated in the pharmacovigilance system.
RLS2: Additional and more active reporting methods are required.
RLS3: Collaboration between pharmacovigilance systems and clinical trials have to be adopted.
RLS4: Effective communication and feedback channels have to be adopted.
RLS5: Patient involvement during the reporting stage should be adopted.
RLS6: A context-specific PV system needs to exist.
<ul style="list-style-type: none"> • The system needs to be region specific and take the specific environments' needs into account. • Specific populations/patients need to be considered when setting up a pharmacovigilance system.
RLS7: The reporting process should be context-specific to the resources available.
<ul style="list-style-type: none"> • Innovative ways are required of capturing data in resource limited settings. • The reports should be available in the local languages of the region/country. • The ADR reporting process should be easy to complete, non-time consuming and friendly to RLS.
RLS8: Reporting should be made compulsory and form part of HCP corporate responsibility.
<ul style="list-style-type: none"> • Non-monetary forms of remuneration should be considered for compensation.
RLS9: A national strategy with respect to PV should be adopted

4.7 CHAPTER 4 CONCLUSION

In this chapter, the requirement analysis process of the systems engineering approach was conducted in order to identify what requirements would be called for by an a context-specific PV system for the MPP drug provision systems. It was established that the minimum requirements for an effective PV systems were inadequate in addressing the unique challenges associated with the niche factors within the context of PV. Thus a three step-approach was conducted to develop a requirement specification that will guide the development of a decision support tool that facilitates the development of context-specific PV systems.

In the following chapter, the next phase of the systems engineering approach, the functional analysis, will be conducted; this entails identifying different intervention strategies that will address the requirement specification, and guide the development of a decision support tool that would facilitate the development of a context-specific PV system.

Chapter 5: Vigilance System Component-Intervention Index development

In a systems engineering process, the aim is to contextualise a problem in order to develop a solution (United States Government, 2001). Within the context of this research inquiry, the particular research problem, namely, the absence of an effective PV system to meet the unique needs called for by the MPP drug provision systems, is addressed by proposing a decision support tool that facilitates the development of context-specific PV systems.

At this stage of the research, the first two phases of the system engineering approach, which entailed contextualising the research problem and addressing the requirements of a context-specific PV systems, have been completed. During the contextualisation of the problem, four niche factors were identified: (i) the traditional PV system, (ii) the MPP, (iii) HIV, TB and Hepatitis C, and (iv) RLS. Furthermore, to ensure that a proposed decision support tool would address and consider the challenges associated with the context of MPP drug provision systems, a challenges landscape pertaining to the niche factors and the pharmaceutical value chain was developed. This challenges landscape is referred to as the PVCCL and is discussed in Chapter 3. The second phase entailed conducting a requirements analysis using insights gained from the PVCCL, the literature, and a verification process, which led to the development of a requirement specification for said system as discussed in Chapter 4.

In this chapter, the functional analysis phase of the system engineering approach is conducted; this entails addressing the developed requirements specification by identifying intervention strategies that can address this set of requirements (United States Government, 2001).

In this chapter, the approach used to identify the intervention strategies will be discussed, along with the process of synthesising the intervention strategies into an index that will guide the development of a decision support tool that facilitates the development of context-specific PV systems. This phase of the research, and how it relates to the rest of the research study, is shown in Figure 5.1.

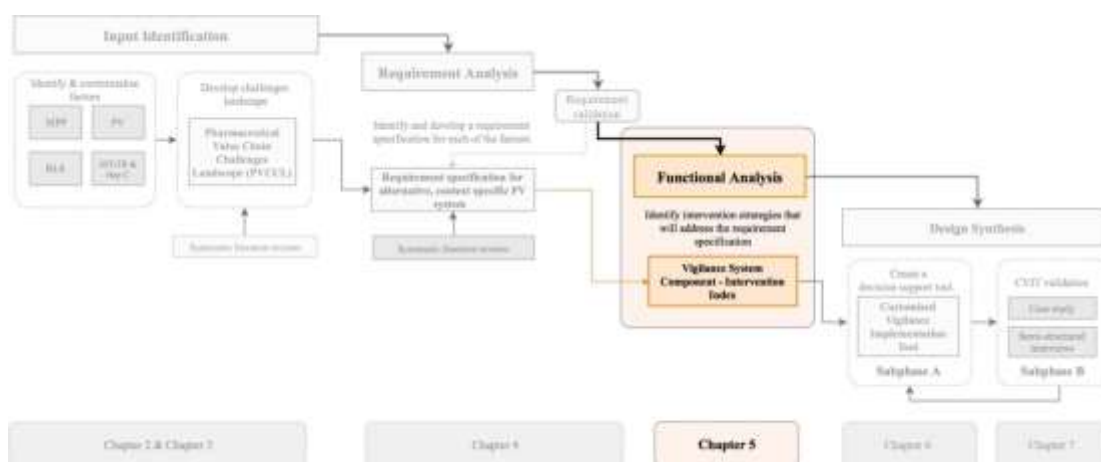


Figure 5.1: Systems engineering: Functional analysis approach

5.1 FUNCTIONAL ANALYSIS APPROACH

A functional analysis is a process, where the system is defined in terms of its functions by translating the requirements into operational functions (United States Government, 2001). The aim of the functional analysis within the context of this research inquiry is thus to identify these operational functions, referred to as the intervention strategies, which will address the requirement specification, and subsequently form the foundational features of a decision support tool. The primary objective of such a system is that it has to operate effectively in the context of an MPP drug provision system, with reference to the effective reporting of ADRs.

The functional analysis is conducted by using the method of triangulation. Triangulation is the practice of using multiple sources and approaches to enhance the credibility of the research (Hastings, 2012). The triangulation method was conducted using the following approaches to identify possible intervention strategies: (i) consulting the literature by considering the requirement specifications (see Section 4.6), (ii) using knowledge gained from observations and real-world phenomena, (iii) and entering into discussion with SMEs.

The first approach entailed using insights gained from the literature regarding the requirement specification. This involved consulting previously identified literature that was used during the development of the requirement specification, Chapter 4, to identify possible intervention strategies. During the functional analysis, intervention strategies were identified by decomposing the higher level requirements, i.e. the entire developed requirement specification, into the lower-level requirements, i.e. each specific requirement called for by the factors, requirements (PV1 – PV1), (MPP1 – MPP6), (RLS1 – RLS9), and (D1-D9), refer to Table 4.11 - Table 4.15. Each of the lower-level requirements was individually considered and possible interventions strategies that would address the requirements in question, were identified. Furthermore, additional literature reviews were also conducted to investigate these intervention strategies.

The second approach entailed using knowledge from a systems engineering and PV perspective, as well as from observing real world phenomena, to identify possible interventions for each of the requirements identified. This entailed addressing each of the requirements individually and identifying all possible interventions to address the requirement in question, similar to the previous approach.

The last approach entailed entering into continuous discussions with SMEs in the field of pharmacovigilance. Although the SMEs come from different backgrounds, they all have knowledge and experience in the field of pharmacovigilance. The first SME has a Bachelor Degree in Medicine and has been the director of the International Society of Pharmacovigilance (ISoP), and is currently a board member of ISOP the International Society of Pharmacovigilance since 2016. The second SME is a PhD candidate from Oxford with an MPharm degree, who is one of the coordinators for Global website, organised and funded by The Global Health Network¹⁶.

Using this triangulation method, a total of 45 intervention strategies were identified that could address the different requirements, as stated in Chapter 4. However, when analysing and

¹⁶ The Global Health Network is a global platform that encourages research through sharing knowledge and methods (The Global Health Network, 2009).

contextualising these intervention strategies, it was ascertained that certain intervention strategies were related to one another due to being linked to similar outcomes and/or objectives with reference to the requirement specifications. Thus, these intervention strategies could be grouped together to create a structure of overarching components that should be addressed when considering the implementation of a context-specific PV system (this is discussed in more detail in Section 5.2). Furthermore, from these groupings of the intervention strategies, i.e. from the overarching components, an index guide for the implementation of a context-specific PV system could be derived.

The process of developing this index guide, along with a discussion of the components and intervention strategies will be provided in the following section.

5.2 VIGILANCE SYSTEM COMPONENT-INTERVENTION INDEX OVERVIEW

During the functional analysis approach, it was ascertained that an index guide could be developed that provides an overview of the various components and respective intervention strategies that should be addressed when implementing a context-specific PV system.

Furthermore, building on the findings it is deduced that a *Vigilance System* should be proposed as a context-specific PV system. A Vigilance System is defined as a context-specific PV system for MPP drug provision systems that assists with the effective and efficient reporting of ADRs through the development of a decision support tool. Furthermore, the Vigilance System address the niche i.e. (i) traditional PV systems, (ii) the MPP, (iii) the HIV, TB and Hepatitis C, and (iv) RLS, throughout the entire pharmaceutical value chain. The development of a Vigilance System is proposed through the creation of an index guide – the Vigilance System Component-Intervention Index - which provides an overview of the various components and respective intervention strategies that should be considered for the implementation of a Vigilance System.

In this section, the development of the index with respect to the contextualisation of the intervention strategies and the overarching components is considered, by discussing the approach and the relationship diagram, which indicates the relations between the different intervention strategies and overarching components with respect to the requirement specification.

5.2.1 Vigilance System Component-Intervention Index development approach

Using the method of triangulation, 45 intervention strategies were identified. These range from solutions that can be implemented in different social and economic environments, i.e. in developing or developed countries, in places without a previous infrastructure or high level of organisation; they are all aimed at addressing the requirement specifications, as stated in Chapter 4. However, after investigating these intervention strategies, it was found that certain intervention strategies could be grouped together based on similar outcomes and/or objective. Furthermore, when considering these grouped intervention strategies and their similar objectives, it was found that they could be synthesised into overarching components that should be addressed when implementing a Vigilance System (see relationship diagram in Section 5.2.2 for a more detailed discussion on this). Thus, within the context of this research study, 10 overarching components with their subsequent group of intervention strategies were

identified. These 10 components are referred to as the *Vigilance System components* and they are:

- i. Mode of reporting;
- ii. Reporting process;
- iii. Databases;
- iv. Response strategy;
- v. Awareness;
- vi. Communication;
- vii. Education;
- viii. Quality management;
- ix. Responsibility & accountability; and
- x. Novel technologies.

These 10 Vigilance System components are discussed in more detail in Section 5.3. Furthermore, as these Vigilance System components are derived from the groupings of the identified intervention strategies, which address the requirement specification, the Vigilance System components subsequently also address these requirements too.

Furthermore, in order to provide a more detailed explanation of the development of these Vigilance System components with respect to the grouping and synthesising of the intervention strategies, a relationship diagram is developed and discussed in the following section.

5.2.2 Relationship diagram

In order to provide more clarity and insight on the development of the 10 Vigilance System components, with respect to the grouping of the intervention strategies, a relationship diagram is developed. This relationship diagram provides an overview of the different identified intervention strategies and which of the requirements, as stated in the Vigilance System requirement specification in Chapter 4, the applicable intervention strategy addresses. Furthermore, the relationship diagram also gives insight into the development of the Vigilance System components, by grouping the intervention strategies based on them achieving similar outcomes and/or objectives with reference to the requirement specification. Refer to Figure 5.2.

Referring to the relationship diagram when considering the different intervention strategies within the context of the specific requirements addressed by said intervention strategy, it emerged that certain intervention strategies addressed the same requirements. For example, referring to Figure 5.2, when considering the following intervention strategies: (i) learning centres, (ii) patient information cards, (iii) paper-based resources, (iv) PV curriculum, (v) short courses, (vi) social media networks and (vii) web-based learning, it was found that all seven of these intervention strategies address requirements PV1, MPP1, D1 and RLS1. Thus, because these intervention strategies fulfil or share the same outcomes, it was decided to group them together in order to develop the component of education (Component 7, Section 5.3.7). The same approach was used for the other intervention strategies and thus the overarching

components, the Vigilance System components, were synthesised. These components are indicated using the colour-key as shown in Figure 5.2. Furthermore, when investigating the relationships, with respect to the intervention strategies that shared similar outcomes within the context of the requirements, it was found that certain requirements addressed multiple different requirements and thus can be related to different Vigilance System components. For example, when considering the component of web-based learning, it was found that this intervention strategy addresses both PV8 and PV7, which are related to the components of mode of reporting (orange) (Component 1, Section 5.3.1) as well as to PV1, MPP1, D1, and RLS1, which are associated with the component of education (green) (Component 7, Section 5.3.7). Thus, when investigating the intervention strategies, the following strategies were found to be associated with more than one component: (i) paper-based resources (ii) policy, (iii) social networks, and (iv) web-based resources. Moreover, each of these intervention strategies is also applicable to the different components within the context of addressing the same requirements.

Based on these findings, and as discussed in Section 5.2.1, an index was developed with the aim to guide the implementation of a Vigilance System by providing an overview of the various components and associated intervention strategies to be addressed when considering a Vigilance System.

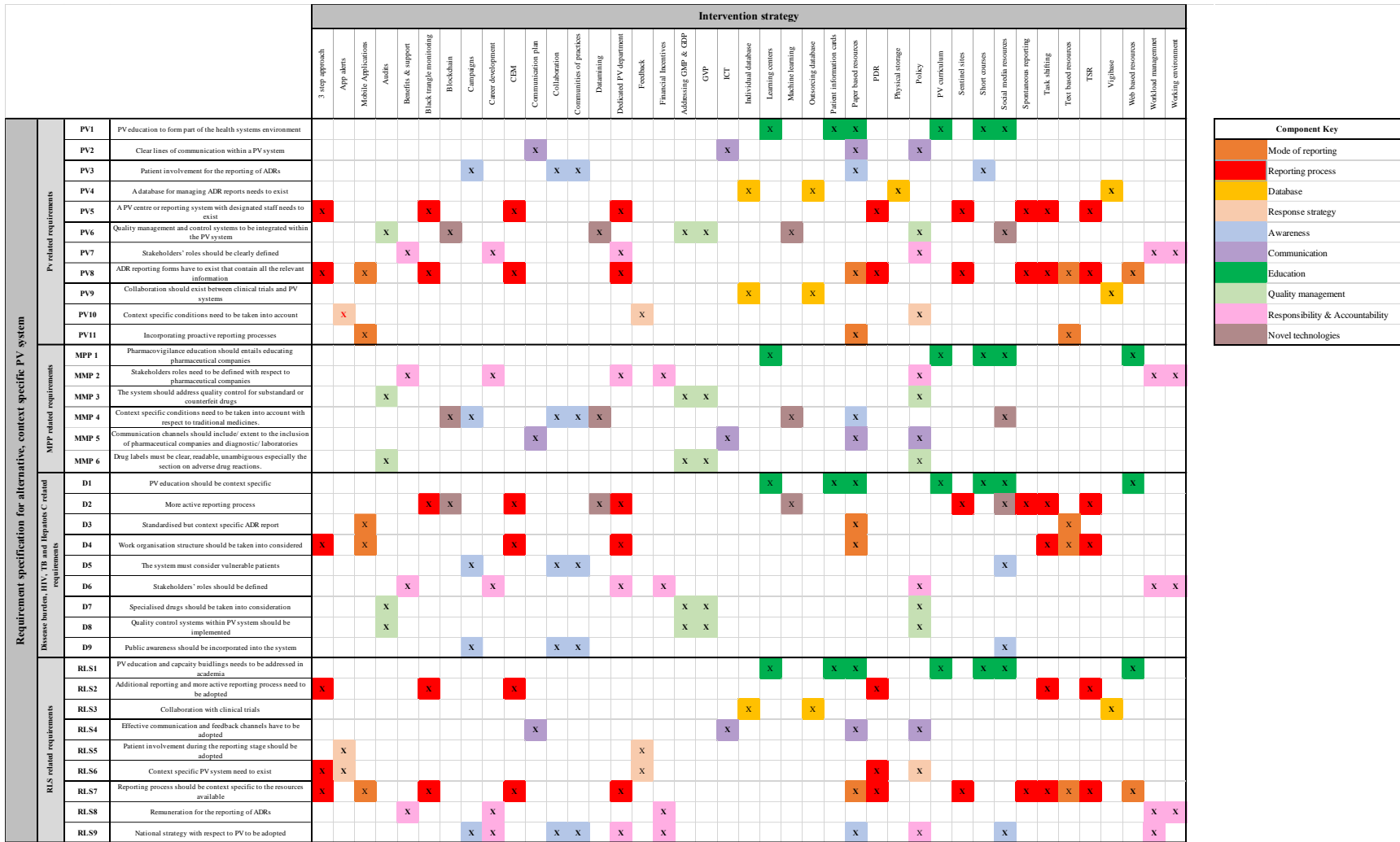


Figure 5.2: Relationship diagram for intervention strategies, components and requirements

5.2.3 Vigilance System Component-Intervention Index

Vigilance system components and their associated intervention strategies were identified and synthesised to develop an index that addresses all the developed requirement specifications, and subsequently provides the foundational concepts for the development of a decisions support tool that facilitates the development of a Vigilance System.

However, when considering the Vigilance System components and taking into consideration the environment of the MPP drug provision systems, which addresses the niche factors and the associated challenges (see Chapters 2 and 3) within the context of the entire pharmaceutical value chain, it was found that the different Vigilance System components could be clustered into three larger categories, namely: (i) direct components, (ii) supporting components, and (iii) additional factors.

The direct components refer to the components required within a PV system that directly affect the reporting, managing and processing of the reported ADRs. These direct components consist of: (i) mode of reporting, (ii) reporting process, (iii) database, and (iv) response strategy and feedback. The supporting components refer to the components and intervention strategies that assist with the effectiveness of the system. The vigilant system components that fall under this category are: (i) awareness, (ii) communication, (iii) education, (iv) quality, (v) management, and (vi) responsibility and accountability. Lastly, novel technologies are grouped under ‘additional factors’, as these do not directly influence the reporting process, nor do they support the effectiveness of the system; rather, they provide the system with an agile component that focuses on the future of PV systems.

The Vigilance System components, along with their associated intervention strategies within their different groupings, form the basis of the index referred to as the *Vigilance System Component – Intervention Index* (see Figure 5.3). This index thus provides an overview of the various components and associated intervention strategies to be addressed in a Vigilance System, and will be synthesised to form the foundational concepts of a decision support tool for the implementation of said system.

In the following section, the Vigilance System Component-Intervention Index will be discussed according to the index’s elements i.e. the various Vigilance System components and their associated intervention strategies.

5.3 VIGILANCE SYSTEM COMPONENT-INTERVENTION INDEX ELEMENTS

As mentioned, the Vigilance System Component-Intervention Index consists of three component categories, each with their associated Vigilance System components and intervention strategies. In this section, therefore, the various Vigilance System components and their respective associated group of intervention strategies are discussed.

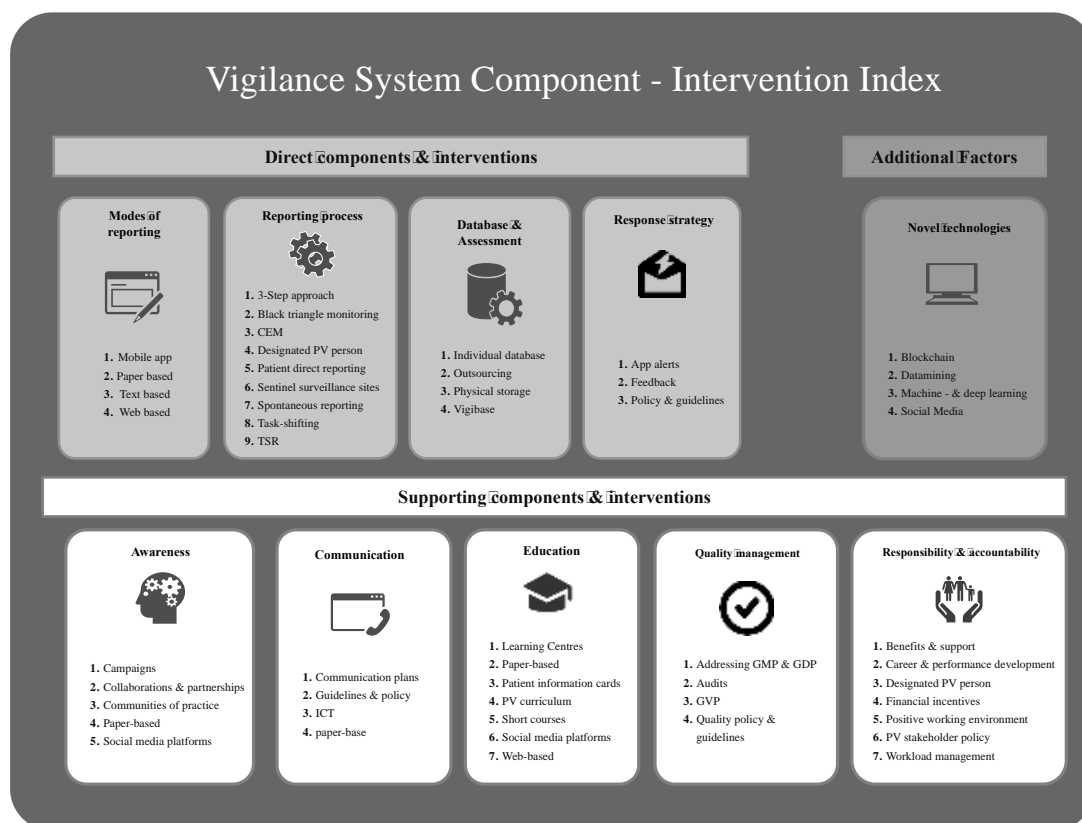


Figure 5.3: Vigilance System Component – Intervention Index

5.3.1 Component 1: Modes of reporting

Within the context of this research inquiry, the phrase ‘mode of reporting’ refers to the form used for the reporting of ADRs. One of the minimum requirements for a functioning PV system, as stated by the WHO, is that the system must have a functioning reporting system with a national ADR reporting form (WHO and The Global Fund, 2010). However, there are various modes in which such an ADR form can be offered.

5.3.1.1 Interventions identified for Component 1: Modes of reporting

Four intervention strategies were identified that are associated with this component namely: (i) mobile application reporting, (ii) paper-based reporting forms, (iii) text-based monitoring, and (iv) web-based reporting. Each of these intervention strategies is discussed in the following subsections.

Mobile application reporting

With the emerging growth of mobile technologies, new opportunities to improve and address problem areas in the healthcare environment are being proposed (Haque *et al.*, 2017), and thus the field of mobile Health (mHealth) is rapidly growing. This intervention provides alternatives and/or solutions to challenges such as limited resources, uneducated or untrained staff and poor health information systems (Aranda-Jan, Mohutsiwa-Dibe and Loukanova, 2014). Mobile Health refers to the use of mobile communication technologies in healthcare environments to promote and support health practices, i.e. data collection, delivery of

information, provision of care, and patient observation (Mechael, 2009; Aranda-Jan, Mohutsiwa-Dibe and Loukanova, 2014).

A popular form of mHealth to consider in the context of this research study, is the use of mobile applications to report ADRs. In India, the Pharmacovigilance Programme of India launched a project that used Android mobile applications to report ADRs (Kuchya *et al.*, 2016). This method is a paperless, quick and relatively uncomplicated way of reporting and managing ADR reports. The app uses simple techniques to prompt the user to enter information (reporter information and information on the suspected adverse event); once the data is captured, it is sent to the monitoring centre. The reporter also receives verification that the report has been received, thus facilitating an effective feedback system. Using built-in algorithms, the report is analysed using a causality assessment based on criteria of the WHO; in the case of severe adverse events, the report is sent via the right channels to the relevant parties to take further action (Kuchya *et al.*, 2016). Mobile application tools in the healthcare environment have also been used to address other problem areas, such as TB contact tracing in Botswana (Ha *et al.*, 2016).

When considering the implementation of mHealth within the context of RLS, however, access to mobile phones and connectivity needs to be considered, particularly as this study addresses the development of a PV system in these environments. Global usage of and access to mobile technology is growing around the world, and according to a Gallup World poll done in 2017, 79% of adults had access to mobile devices even in RLS, thus affirming that this intervention strategy can be a viable option (Spotlight, 2017).

Paper based reporting forms

This mode of reporting entails using paper-based forms, which require the patient or HCP to complete a form and send it to the corresponding authority via post, facsimile (SCOPE and MHRA, 2015). Paper-based reports are often found to be one of the most common and easiest forms of reporting. The management of these reports, however, does prove a challenge, as the management, distribution and extraction of data can be more resource inefficient than using information technology communications, such as web-based or mobile-based approaches (Almenoff, 2007; SCOPE and MHRA, 2015).

Text-based monitoring

Another form of mHealth to consider for ADR reporting is text-based reporting. A study was done in Cambodia on the use of a text message-based PV Tools. This pilot project, using FrontlineSMS¹⁷, which commenced in 2012, was one of the first SMS text-based reporting and surveillance systems for ADR detection (Baron *et al.*, 2013). The objective of the project was to test if vaccine adverse events could be reported in an effective and timely manner to a vaccine centre. The systems run through a software operation that received responses, analyses these and provides adequate replies back to the user based on their response. For example, if a user reports a severe adverse event (based on a rating of codes), the system prompted a message to the user to consult medical assistance as required (Baron *et al.*, 2013). This pilot

¹⁷ FrontlineSMS is an open source software used to collect and analyse information received through text messages (SMS). The platform has been used by a variety of organisations.

project, although small and limited, showed very favourable results when considering drug safety monitoring in urban and resource limited settings.

Furthermore, studies also indicate that text messages are more likely to work effectively if there is follow-up with the users, the messages are more personally tailored, and the content is relevant to the patient (Tomlinson *et al.*, 2013). The use of text message-based surveillance can be seen as a possible intervention for the Vigilance System, and using simple software, such as FrontlineSMS, can be a very useful tool to address challenges (Baron *et al.*, 2013; Tomlinson *et al.*, 2013).

Web-based reporting

Web-based reporting is similar in nature to mobile application reporting; in the context of this study, it refers to website-based reporting on a desktop, laptop or tablet. Electronic ADR reporting forms or online platforms are the most commonly used mode of reporting ADRs in both developing and developed countries (Medicines & Healthcare Agency Regulatory (MHRA), 2019). Using an online platform is an efficient and cost-effective mode of reporting, that does not require an extensive amount of resources. Furthermore, these online platforms can be adapted and customised for specific niche environments and cases (Edwards, 2019; Medicines & Healthcare Agency Regulatory (MHRA), 2019).

One such an online reporting platform used in the UK is the Yellow Card scheme¹⁸. This platform allows HCP and members of the public to report suspected ADRs (Medicines & Healthcare Agency Regulatory (MHRA), 2019). It also makes available reporting forms for adverse effects related to medical devices, suspected counterfeit medications, and side effects related to e-cigarettes.

5.3.2 Component 2: Reporting process

Reporting process in the context of this research inquiry refers to the ADR process associated with the capturing of the data, and the processing thereof. The WHO states that one of the minimum requirements for a functional PV system is to have a functioning national spontaneous reporting system (WHO and The Global Fund, 2010). Thus, one of the basic fundamentals of a working PV system is to have an effective system for the reporting of ADRs.

5.3.2.1 Interventions identified for Component 2: Reporting process

The following nine reporting intervention strategies were identified and will be discussed in more detail below: (i) 3-step approach, (ii) black triangle monitoring, (iii) cohort event monitoring (CEM), (iv) dedicated PV person/department, (v) patient direct reporting, (vi) sentinel surveillance sites, (vii) spontaneous reporting, (viii) targeted spontaneous reporting, and (ix) task shifting.

3-step approach

The 3-step approach of reporting ADRs and collecting data is found to be very effective in RLS, which is defined as having limited numbers of qualified HCP and low levels of PV knowledge, as stated in Section 3.2 (Mudzviti *et al.*, 2013). This approach looks at utilising different stakeholders for each of the different practices of the reporting process. The first step

¹⁸ Website: <https://yellowcard.mhra.gov.uk/>.

refers to using any available individuals, no qualification needed, to capture the data by filling out a form with the patient. The second step requires a clinically qualified HCP, such as a pharmacist or nurse, to collect the data from the various treatment centres, and the third step is to then submit the data to the necessary central body, such as the National PV centre or WHO (Mudzviti *et al.*, 2013; Edwards, 2019).

Black triangle monitoring

Black triangle monitoring was introduced by the EU European Medicines agency, for drugs that require additional or more intensive monitoring by regulatory authorities, such as SAHPRA (European Medicines Agency, 2013). More intensive monitoring is required for these drugs, often because there is less safety information available about them, or because these drugs may contain a new active substance, or because the drug may only have been approved under exceptional circumstances, or because it is a ‘biological medicine’¹⁹. Furthermore, black triangle monitoring is also often exercised in cases where the manufacturing company is required to perform additional monitoring due to the occurrence of a rare side effect that was identified during the clinical trial phase (Martin *et al.*, 1998; Zun, 2014). Drugs under black triangle monitoring are denoted with a black inverted triangle (▼) often with a short explanatory sentence. The black triangle does not mean the drug is unsafe for patient usage, but merely highlights that the safety information related to the drug is being advised (Martin *et al.*, 1998; European Medicines Agency, 2013).

Cohort Event Monitoring

Cohort Event Monitoring (CEM) is an active²⁰ form of PV that is used to monitor ADRs in patients who are receiving a specific treatment regime in order to assess causality (Wallberg, 2009; Pal *et al.*, 2013). CEM involves actively following up with a cohort of patients to register all ADRs that occur during and for a period after the patients’ treatment (Wallberg, 2009). However, CEM also captures all other medicine-related events, from medication errors, issues caused by poor storage conditions, poor quality drugs, counterfeit drugs, and drug interactions, and it records all events regardless of their severity. This PV method is specifically applicable during the early stages of exposure to a new medicine in the field, as it is a systematic and comparable method of monitoring. CEM does not only contribute to risk management of drugs, but can also provide insights into utilisation and adoption patterns of drugs. CEM has also been effectively implemented in both low- and high-income countries. The WHO has developed a detailed handbook that sets out the principles of CEM and its implementation in the public health programmes (Pal *et al.*, 2013; WHO, 2015a).

Designated PV person/department

This initiative is aimed at introducing a dedicated department to the reporting and other PV related processes. In RLS, HCP often have a heavy workload, and thus reporting of ADRs is often considered a redundant task (Edwards, 2019; Walker, 2019). A person or a department designated to deal with PV may thus be introduced into the healthcare facilities with the sole responsibility of addressing all PV related areas, from reporting of ADRs, to the providing of

¹⁹ Biological medicines are medicines or vaccines that have been derived from blood plasma.

²⁰ In an active PV surveillance approach, patients are monitored systematically in order to gain detailed information of a patient’s ADR encounter, whereas passive surveillance allows HCP to voluntarily report incidences, such as ADRs, within their environment (Pohlman *et al.*, 2017).

feedback and follow-up with patients (Rachlis *et al.*, 2016; Edwards, 2019). The department staff would have to come from a medical background, to assist with the ADR detection, and would be required to have or receive PV education with reference to the identification and reporting of ADRs (Rachlis *et al.*, 2016; Edwards, 2019).

Patient direct reporting

Patient direct reporting (PDR) of ADRs was introduced in Denmark and the Netherlands in 2003 (Delaney, 2017). To date the most commonly used forms of PDR are by using mobile applications, such as the UK's Yellow Card Scheme, which is originally a paper-based scheme that was adapted to an online platform, and that is directly linked to the databases, such as the Upsala reporting database Vigibase²¹, thus providing the public with basic access to the database (Anderson *et al.*, 2011; Delaney, 2017).

Sentinel surveillance sites

Sentinel surveillance is another active form of reporting that is used when higher quality data is required about a specific disease (Management Sciences for Health (MSH), 2010; Olsson *et al.*, 2010; Miller, Nwokike and Stergachis, 2012). It operates by selecting specific reporting units that have a higher probability of addressing cases about the illness under consideration and that have highly qualified and experienced staff (Miller, Nwokike and Stergachis, 2012). Whereas passive systems, such as spontaneous reporting, focus on retrieving data from as many health care facilities as possible, a sentinel site purposefully only involves a limited, specific network of healthcare facilities (Management Sciences for Health (MSH), 2010; Olsson *et al.*, 2010). As sentinel sites often do not represent the general population, a limitation is that of generalising national disease patterns. However, there are additional advantages to the implementation of sentinel sites. More feedback and supervision can be provided, as sentinel sites are located in fewer facilities, which again leads to higher quality data being obtained. Sentinel sites are often also less expensive to run and maintain when compared to a universal reporting system (Management Sciences for Health (MSH), 2010).

Targeted spontaneous reporting

Spontaneous reporting is a universally used method that HCP, drug manufacturers, and patients use to report ADRs to national PV coordinating centres (Masenyetse, Manda and Mwambi, 2015). It provides the highest volume of information at the lowest cost. Spontaneous reporting provides early signal detection of a potentially problematic medication, which leads to further investigation, regulatory warnings or even product changes. Spontaneous reporting, as mentioned, is a passive form of reporting and thus relies on the initiative of the patient to report an ADR. Furthermore, as there are no systematic patient follow-ups, clear protocols or PV mandates, it is challenging to determine the accurate rates and frequencies of ADRs experienced (Pal *et al.*, 2013; Masenyetse, Manda and Mwambi, 2015). Thus, spontaneous reporting is more effective when it is combined with additional reporting processes (Pal *et al.*, 2013).

²¹ Vigibase is a database system used for data management and processing that is operated by the UMC.

Task shifting

A study by Olsson et al. (2015) found that, in RLS, the patient records are often lost or incomplete and thus can often not be used to extract information about a reported ADR at a later stage (WHO, 2007b; Olsson, Pal and Dodoo, 2015a; Prasad *et al.*, 2018). This means that the reports have to be filled out at the time of the consultation, which creates an additional challenge in RLS environments, as the patient to physician ratio is very low (WHO, 2007b; Olsson, Pal and Dodoo, 2015a). Thus, tasks such as completing ADR reports and collecting data should be ‘task-shifted’ to other HCP, such as nurses or interns (WHO, 2007b; Olsson, Pal and Dodoo, 2015a). Nonetheless, the ultimate responsibility and accountability would still lie with the physician or the treating HCP (Olsson, Pal and Dodoo, 2015a).

Targeted spontaneous reporting

Targeted spontaneous reporting (TSR) was introduced by the WHO in 2010 and builds on the principles of spontaneous reporting but applied more actively and within a defined setting (Pal *et al.*, 2013; Ndagije, Nambasa and Namagala, 2015; Rachlis *et al.*, 2016; Prasad *et al.*, 2018). This method requires HCP to manage a well-defined patient group, i.e. patients who are being treated for drug resistant TB, for instance, and to report specific medicine related safety concerns. TSR can be customised to either report all suspect ADRs experienced by the group or it can focus on specific reactions that are of particular concern, in order to limit the ADRs to those that are of more significance (Pal *et al.*, 2013; Ndagije, Nambasa and Namagala, 2015). This method is used for targeted follow-up of patients with additional complications, such as drug resistant TB (Pal *et al.*, 2013; Prasad *et al.*, 2018). The benefit of using TSR instead of spontaneous reporting is that the number of patients being managed within the cohort will be known and thus the rates of ADRs being reported will be known (Pal *et al.*, 2013).

5.3.3 Component 3: Databases

One of the fundamental properties of a functioning PV system is to have a national database for the collating and managing of the ADR reports (WHO and The Global Fund, 2010).

5.3.3.1 Intervention identified for Component 3: Database

Four intervention strategies related to databases were identified, namely: (i) individual databases, (ii) outsourcing, (iii) physical storage and (iv) Vigibase.

Individual database

When developing a PV system, a unique database can be created for the specific system that is being developed, that is solely used to manage the data retrieved by that system and to monitor the specific reports gathered (WHO and The Global Fund, 2010; Chakrabarty and Thawani, 2011). This database should be classified, safely stored and managed, retrievable and retain some degree of confidentiality. The WHO and UMC provide guidelines on how to set up commercialised data programmed that can be customised for specific usage (Chakrabarty and Thawani, 2011).

Outsourcing

Various companies, like PrimeVigilance or Oracle, maintain global ADR databases (Arora, 2012; Oracle, 2018; PrimeVigilance, 2019). These companies provide solutions for the

processing, analysing and reporting of ADRs and enable clients to view their data in real time (Edwards, 2008; Arora, 2012). These companies are often employed by pharmaceutical manufacturing companies to manage their own databases of reported ADRs (Edwards, 2008).

Physical storage

In the case of paper-based reporting, the forms need to be stored in a safe space once they have been uploaded to the specific database, as the reports could contain confidential medical information (Almenoff, 2007; SCOPE and MHRA, 2015). The reports need to be disposed of in such a manner that the information is completely destroyed, i.e. by burning or shredding the documents (Almenoff, 2007; SCOPE and MHRA, 2015).

VigiBase

VigiBase²² is a database system used for data management and processing that is operated by the UMC on behalf of the WHO (Lindquist, 2008; UMC, 2019b). Its main aim is to collect and analyse the ADR reports of all members of the 'WHO Drug Monitoring Program'²³. VigiBase comprises medicinal products, the WHO Drug Dictionary, the medical terminology classifications, and the case safety reports that are directly reported to VigiBase. The ICSR are updated on a continuous basis as they are received from the global National PV centres (Lindquist, 2008).

5.3.4 Component 4: Response strategy

Within the context of this research, the response strategy refers to the approach that should be taken once an ADR has been reported. This intervention strategy addresses the methods that should be implemented to ensure that the stakeholders are informed about the report that has been received, the process to follow and in the case of severe or dangerous ADRs, the interventions that will follow to improve patient safety.

5.3.4.1 Interventions identified for component 4: Response strategy

Three interventions were identified related to response strategies. These intervention strategies are: (i) App alerts, (ii) feedback, and (iii) policy and guidelines.

App alerts

An intervention that can be used to provide rapid information flow regarding serious reported cases, is App Alerts. This intervention is aimed at informing HCP, pharmacist and doctors, about drugs that are suspected to cause severe drug reactions or to be of sub-standard quality, by using a mobile application (Edwards, 2019; Walker, 2019). If a specific action regarding a drug needs to be taken, the necessary stakeholders would be alerted via the mobile app. The focus of the alert is only to inform an HCP, if immediate action needs to be taken. The app alerts should work on a severity scale, i.e. only provide an alert if a drug has had a high volume of reports in a specific time frame (Edwards, 2019; Walker, 2019).

²² Website: <https://www.who-umc.org/vigibase/vigibase/>

²³ This is a group of more than 150 countries worldwide that work nationally but collaborate internationally to monitor drug safety and to establish a world-wide pharmacovigilance system.

Feedback

In any reporting system, it is essential that the stakeholders, including patients, receive feedback (WHO, 2006b). This feedback should confirm that the report has been received and, if needed, the actions to be taken. In a PV system, it is crucial to give feedback to the reporter of the ADR, as under-reporting of ADRs is often associated with a lack of feedback (Anderson *et al.*, 2011). As mentioned, at the very least a confirmation of receiving the ADR report is required; however, a study on direct reporting by patients found that patients often have a need for more information regarding their reported ADR, and not only to receive confirmation (Anderson *et al.*, 2011). For example, patients would like to be informed if the report has contributed in some way, if more reports were received and, if necessary, what action has been taken (WHO, 2006b). The following modes of providing feedback were identified and will be discussed below: (i) emails, (ii) mobile platforms, (iii) web-based platforms, and (iv) paper-based responses.

The usage of emails and mobile phones is very high globally, and thus these forms of technology of providing feedback can be very effective in both developed and developing countries (Spotlight, 2017). To ensure that there is continuous communication between the reporter and the PV centre regarding further steps to be taken, the reporter should be allowed the opportunity to access additional information and be informed about the decision taken with regard to the reported suspected drug (Edwards, 2019). Web-based platforms, such as VigiAccess²⁴, which allow members of the public access to information about the amount or reports received and the list of ADRs reported for every drug, is such an intervention (UMC, 2019).

Another mode to consider for providing feedback would be to use paper-based resources, such as formal letters or newsletters (Almenoff, 2007; Vermeir *et al.*, 2015). Formal letters can be distributed using postal services, whilst newsletters that provide information about the reported ADRs can be distributed to healthcare facilities. However, these forms of reporting will be more resource intensive and will take longer to reach the recipient.

Policy and guidelines

Guidelines need to be created to ensure that there is an effective, feasible response strategy in place for when a suspect drug has been identified and needs to undergo further monitoring, or when further action needs to be taken, such as removing the drug from the market entirely. The guidelines need to be clear about the exact steps that need to be taken by each of the stakeholders during the response strategy (U. Mehta *et al.*, 2014; Edwards, 2019). These guidelines should stipulate the actions that pharmaceutical manufacturing companies need to take when a drug needs to be monitored more carefully or be taken off the market (WHO, 2002c; Mehta, Allen, *et al.*, 2014).

5.3.5 Component 5: Awareness

Creating a culture of PV and drug safety monitoring is of the utmost importance, as it will improve the challenges recognised in the reporting process with regard to ADR detection, under-reporting, and the quality of data (Dennison, Wu and Ickes, 2014; Lamprecht, Bam and

²⁴ Website: <http://www.vigiaccess.org/>

De Kock, 2017). Thus, improving both the public's and the HCP's awareness of the importance of PV should form an integral part of a Vigilance System.

5.3.5.1 Interventions identified for component 5: Awareness

The following five awareness related interventions were identified and will be discussed below: (i) campaigns, (ii) collaboration and partnerships, (iii) communities of practice, (iv) paper-based resources, and (v) social media platforms.

Campaigns

A campaign consists of a series of planned events and activities aimed at achieving a specific objective (Steurbaut and Hanssens, 2014; BusinessDictionary, 2019). Campaigns share a single message and aim to convey that message to a target audience (Steurbaut and Hanssens, 2014). In 2015, the UMC initiated a campaign, Take & Tell²⁵, with the focus of making PV a household concept. The Take & Tell campaign was aimed at improving the public's knowledge about PV by informing patients about how to report a possible side-effect (Upsala Monitoring Centre, 2019). The objectives of the campaign were thus to create awareness about PV, to create open communication between patients and HCP, and to support the active reporting of ADRs (Montastruc *et al.*, 2006; Steurbaut and Hanssens, 2014; Upsala Monitoring Centre, 2019).

Collaboration and partnerships

Collaborating and partnering with existing PV bodies, healthcare facilities and pharmaceutical companies can be an effective strategy to engage with people and create awareness about PV with different stakeholders. Advocating the importance of PV can be conducted by creating and fostering partnerships with different stakeholders. The different pharmaceutical industries, pharmaceutical manufacturers and PV bodies could partner with one another to improve patient safety and drug safety monitoring (Schito *et al.*, 2015). Partnership policies can be created that define the agreement between the partners and stipulate the agreed upon objectives the partnership needs to fulfil with regard to improving PV awareness (Schito *et al.*, 2015; Edwards, 2019).

Communities of practice

Improving the awareness of PV and a PV culture within the public, focusing on patients, can be achieved through community involvement projects (Dennison, Wu and Ickes, 2014). This can be done by including patients and/or stakeholders into the different phases of the system and incorporating effective channels of communication to ensure the patients' needs can be addressed (Edwards, 2019). Furthermore, awareness campaigns focus on conveying a message to educate and raise public interest and knowledge about the subject matter, in order to improve community involvement (Dennison, Wu and Ickes, 2014).

Paper-based resources

Paper-based resources can be effective in creating awareness, considering the context of this research (Almenoff, 2007). A study published in the *Health Information and Libraries Journal* found that posters are not only some of the most commonly used forms of providing information

²⁵ <http://www.takeandtell.org/#takeandtell>

in the healthcare field, but may also contribute towards altering behaviour and attitudes (Ilic and Rowe, 2013). Thus, using paper-based resources to create a culture of PV and ADR reporting can be very effective, especially in RLS (Almenoff *et al.*, 2007; Ilic and Rowe, 2013). Furthermore, the most effective awareness campaigns are aimed at evoking emotions in readers, and thus using tactics such as statistics, images and slogans would improve the impact of the campaign (Ilic and Rowe, 2013).

Social media platforms

As previously mentioned, social media platforms are expanding and are being utilised in many different fields for different purposes (Sloane, Osanlou and Lewis, 2015). Social media can thus be a vital instrument for improving awareness on PV in the healthcare and public environments. Platforms such as YouTube, Twitter, Facebook, and LinkedIn can all be used as platforms to create awareness on the importance of ADR reporting and PV (Sloane, Osanlou and Lewis, 2015; Edwards, 2019; Walker, 2019).

5.3.6 Component 6: Communication

In a PV system, there are various stakeholders who all play a vital role in the system. However, as mentioned, the challenge of not having effective channels of communication often leads to further complications, such as a loss of information (Mehta, Dheda, Steel, M. Blockman, *et al.*, 2014). Thus, interventions are needed to create, improve, enhance and maintain communication channels between the different stakeholders.

5.3.6.1 Interventions identified for component 6: Communication

Four communication interventions were identified: (i) communication network plans, (ii) information communication technologies (ICTs), (iii), guidelines and policies, and (iv) paper-based resources.

Communication network plans

Ensuring that there is an effective communication network plan, which indicates a flow of information between the different stakeholders, is vital to ensure that the different stakeholders react appropriately to the emergence of an event, i.e., emerging new safety data regarding ADRs (Bahri, 2010). The communication network plan should give an overview of the different communication channels that have to exist between the different stakeholders. Furthermore, the communication network plan should specify the flow of information and communication tool used (Bahri, 2010).

Information Communication Technologies

ICTs are technologies, such as the internet, wireless and cellular networks, that use telecommunication to provide access to information (TechTerms, no date; Lu, 2009).

ICTs can be an effective intervention and communication tool used by different stakeholders for different PV objectives, from reporting to providing feedback and ensuring the flow of information between the different stakeholders. The literature has furthermore argued that ICT has enabled improvements in clinical safety monitoring and PV systems (Lu, 2009).

Possible ICT tools that can be considered for the purpose of this research study with respect to communication purposes are (i) email, (ii) text message applications or short message services (SMS), and (iii) video conferences such as Skype. Within the healthcare environment,

and specifically in PV system, emails have been found to be a very effective form of communication in many different fields and environments (Lhotska *et al.*, 2011). In 2019, Radicati, a technology market research firm, released statistics about global email usage, stating that there are 3.9 billion active email users, which is more than 50% of the entire world's population (The Radicati Group, 2019). Text-message applications are also widely used in both developing and developed countries for the purpose of communicating (Aranda-Jan, Mohutsiwa-Dibe and Loukanova, 2014).

Guidelines and policies

Guidelines and policies can be used to improve communication between the different stakeholders within the PV system (Bahri, 2010). When considering these policies within the context of addressing communication within the proposed Vigilance System, it would be required to stipulate and define the different communication channels between the stakeholders (WHO, 2004; Bahri, 2010). Furthermore, the policies that address these communication channels would also be closely related to the responsibilities of the different stakeholders, as the policies would clarify the information flow and communication between stakeholders (Mehta, Allen, *et al.*, 2014).

Paper based resources

As previously mentioned, in RLS, paper-based forms of communication, and in the environment of PV, paper-based reporting of ADRs, have been shown to be very effective (Almenoff, 2007). Thus, in environments where electronic forms of communication are not a viable option, paper-based communication should be considered instead to ensure the flow of information between the different stakeholders (Almenoff, 2007). According to the WHO (2004), the following forms of paper based communication resources are used within the context of PV: formal letters, patient information leaflets, personal feedback letters to reporters, etc. (WHO, 2004).

5.3.7 Component 7: Education

Within the context of this dissertation, when considering the PVCCL it is evident that there is a lack of education regarding pharmacovigilance and the ADR reporting system within the healthcare setting. This has been more apparent in RLS in healthcare environments (Lumpkin, 2000; Farha *et al.*, 2015; Kheloufi *et al.*, 2017).

5.3.7.1 Interventions identified for component 7: Education

The following interventions were identified, and are discussed below: (i) learning centres, (ii) paper-based resources, (iii) patient information cards, (iv) PV curriculum, (v) short courses, (vi) social media networks, (vii) web-based resources.

Learning centres

The focus of learning centres is to create an environment for collaboration, discussion and teaching opportunities on an increasingly permanent basis, within the context of a physical space, i.e. a PV facility or healthcare facility (WHO, 2012). These learning centres may serve as an environment for PV education by providing and facilitating workshops and training courses. Furthermore, these learning centres can be aimed at different stakeholders within the environment of PV, i.e. HCP, pharmaceutical manufacturers, healthcare students. The learning

centres can, for example, host workshops aimed at students in the pharmaceutical and medical fields, or conferences for experts in the field of PV, or events for all types of audiences (Gerritsen *et al.*, 2011; WHO, 2012).

Paper based resources

Paper-based educational resources, such as pamphlets and posters, can be an effective way of improving education related to PV, ADRs and drug safety monitoring in RLS (Ilic and Rowe, 2013). They can be used to provide necessary and important information about what PV is, why it is needed and how to go about reporting ADRs (Ilic and Rowe, 2013). These paper-based educational resources can be aimed at different target groups, but would probably be the most effective educational resource for educating patients on PV (Ilic and Rowe, 2013).

Patient information cards

Patient information cards are a paper-based method of providing education that are specifically aimed at providing the *patient* with information regarding their specific treatment and possible ADRs (Poirot *et al.*, 2016). These cards contain information on the symptoms of the known ADRs related to the specific diseases, and how and where to report these ADRs (Poirot *et al.*, 2016).

Pharmacovigilance curriculum

As PV is often seen as having a multi-disciplinary nature, as it considers clinical medicines, pharmacoepidemiology, pharmaceutical manufacturing, legal aspects, and molecular mechanisms of ADRs, the structure of the PV curriculum may be overwhelming (Hagemann *et al.*, 2014; Hartman, Härmark and van Puijenbroek, 2017; Edwards, 2019). Consequently, the WHO in collaboration with the International Society of Pharmacovigilance (ISoP) and its Education and Training Project group developed the Pharmacovigilance Curriculum, an existing PV curriculum that is currently in the process of being rolled out (Hagemann *et al.*, 2014). The focus of this curriculum is to provide an overview of PV, to provide information and teachings on new topics in PV, and to propose a range of tasks for practical training (Hagemann *et al.*, 2014).

The developed Pharmacovigilance Curriculum consists of 15 different theoretical chapters that look at the background and history of PV, clinical aspects of ADRs, risks of serious ADRs, quality defects, reporting methods, regulatory bodies, and communication (Hagemann *et al.*, 2014). This curriculum has been developed in such a way that it can be adapted to the specific audience, environment and availability of time (Hagemann *et al.*, 2014).

Short courses

Short courses are an educational intervention that do not require an extensive amount of time and resources that can be used to acquire, update or enhance skills in PV (Dunn and Thorogood, 2002). These short courses can be provided on an online platform or in a physical space such as at a university or at PV centres (Global Pharmacovigilance, no date; Dunn and Thorogood, 2002). The website, Global Pharmacovigilance²⁶, currently offers two free online

²⁶ <https://globalpharmacovigilance.tghn.org/>

short courses (e-learning courses), one on collecting ADR reports, and the other on data safety monitoring (The Global Health Network, 2019a).

Social media networks

As social media networks have expanded significantly and are being used in different domains, it should be considered to use social media as an educational platform for PV (Sloane, Osanlou and Lewis, 2015). For instance, when considering the different social media platforms and the focus of PV education, platforms such as Twitter, Facebook, LinkedIn or YouTube could be utilised for PV educational purposes (Edwards and Lindquist, 2011).

Web based learning

Web-based learning and PV websites can also be used to improve PV education for different audience groups, from HCP to patients. These websites can serve as a platform that links the user to e-learning services, articles and reading materials, and to training or workshops being held (The Global Health Network, 2019b; Walker, 2019). Furthermore, a website can be used as a platform to provide current news and information about pharmacovigilance and drug safety monitoring. Websites, such as that of Global Pharmacovigilance, have proven to be a great success not only for educational purposes, but also for networking, creating awareness and providing information about careers, conferences and events (The Global Health Network, 2019b).

5.3.8 Component 8: Quality Management

In any system, ensuring that effective quality management is integrated within the different processes is of the utmost importance (Olsson, Pal and Dodoo, 2015b). The concept of quality management for the purpose of this research inquiry is concerned with the process related to the reporting and assessing ADRs, but also considers the integration of quality management with the drug manufacturing and distribution systems (Olsson, Pal and Dodoo, 2015b).

5.3.8.1 Interventions identified for component 8: Quality Management

Four quality management intervention were identified for a proposed Vigilance System namely: (i) addressing good manufacturing practices (GMP) and good distribution practices (GDP), (ii) audits, (iii) Good Pharmacovigilance Practices (GVP), and (iv) policies and guidelines.

Addressing good manufacturing practices and good distribution practices

Guidelines for GMP and GDP have been developed by the WHO to ensure consistent quality standards are met in all aspects of drug manufacturing, from material sourcing to the final product (WHO, 2002b, 2011). These guidelines also consider drug safety monitoring aspects (WHO, 2011). Furthermore, the WHO guidelines include guidelines related to complaints, product recalls, quality audits, materials, and training, all of which can be improved to incorporate PV specific aspects (WHO, 2011). The processes of product recall and complaints should be directly linked to PV systems and should stipulate aspects relating to the procedures and communication lines (WHO, 2011). Referring to quality audits and materials, these guidelines should be linked to PV guidelines with regard to the process that should be followed if sub-standard or counterfeit drugs are reported (Pan American Health Organization, 2011; WHO, 2011). With regard to PV training in the GMP, it is necessary that all stakeholders,

including pharmaceutical companies, are also educated on the quality management process within the context of a PV system, which should be stipulated in the GMP (WHO, 2011).

Audits

Audits play a vital role in ensuring that the quality standards are met; as with any system, the PV system also requires regular audits to be conducted (Pietrek, Coulson and Czarnecki, 2009; Nwaiwu, Oyelade and Eze, 2016). During a PV audit, a number of investigations are conducted to ensure that each process meets the required quality standards. The aim is to use evidence to evaluate the PV system and the effectiveness of the system. The audit entails a review of the quality management of the collection, processing and management of the data systems, within the context of ADR reporting and investigation, and assessing whether the database meets the current regulations (Pietrek, Coulson and Czarnecki, 2009; Nwaiwu, Oyelade and Eze, 2016).

Good Pharmacovigilance Practices

The guidelines for Good Pharmacovigilance Practices (GVP) were published in 2010 by the EU and are divided into two main chapters: pharmacovigilance processes and population- and product specific considerations (European Medicines Agency, 2017). The guidelines provide a comprehensive overview of all the relevant aspects with regard to PV and drug safety in general. The guidelines provide best practice information about the collection of the different reports, the validation and follow-up of the reports, and the data management process. Information of the use of medications during pregnancy and for paediatric and elderly patients is also included (Pietrek, Coulson and Czarnecki, 2009; Pan American Health Organization, 2011; European Medicines Agency, 2017).

Policies and guidelines

As previously stated, policies and guidelines are identified as an intervention strategy that could address three of the identified v Vigilance System components, i.e. communication, responsibility and accountability, and quality management. Within this context of quality management, policies and guidelines are aimed at ensuring that the PV processes meet the required quality standards to ensure effective and efficient reporting by using regulation/legislation of said policies (WHO, 2002b, 2004; European Medicines Agency, 2017). To ensure that effective quality management is executed within a Vigilance System, a document, i.e. a policy, which outlines the standard operating procedures within the context of a PV system, i.e. the process related to reporting, collection, management of the ADR related data, should be developed (European Medicines Agency, 2017). The policy should thus stipulate requirements and recommendations within the context of quality management principles that would ensure the effectiveness of the PV process (WHO, 2004).

5.3.9 Component 9: Responsibilities and accountability

Responsibility and accountability are key factors that relate to stakeholder involvement within a PV system (Hanzl-Dujmović, Sulić-Milišić and Starešinić-Šernhorst, 2007; Khattri *et al.*, 2012; Nwaiwu, Oyelade and Eze, 2016). As there are multiple stakeholders involved within the PV system, it is vital that each stakeholder understands their specific role (Edwards, 2019). Responsibility refers to an individual conducting and taking ownership of a specific task, whereas accountability refers to the taking on of a liability and answerability in respect of a

task (Cambridge University Press, 2018, 2018). Thus, it is important to note that there may be a difference between the person, department or institution that is accountable or responsible for a specific process or activity (Edwards, 2019).

5.3.9.1 Interventions identified for Component 9: Responsibility and accountability

Three interventions were identified to ensure that the stakeholders are aware of their roles, and of their accountability and responsibilities associated with such roles; these intervention strategies include: (i) designated PV department/stakeholder, (ii) incentives that contain a subset of four possible intervention strategies, and (iii) policy and guidelines.

Designated PV department/group

Having a designated member of staff, or a designated department that specifically takes on the role of accountability of ADR reporting within the healthcare facility would not only reduce the workload of the HCP but will also address the concept of accountability, as there would be a specific group or individual that takes on all aspects of PV (Rachlis *et al.*, 2016; Edwards, 2019). As this department would be responsible for all PV related functions, the margin of error in the reporting process would also be reduced and the process of follow-up on actions to be taken with respect to the suspected ADR would be easier (Edwards, 2019; Walker, 2019). Furthermore, this concept of designated PV staff members or departments can also be introduced to pharmaceutical manufacturing companies to improve the relationships, communication, and responsibility of pharmaceutical manufacturing companies with the PV centres and healthcare facilities (Rachlis *et al.*, 2016; Edwards, 2019).

Incentives schemes

In the healthcare landscape, incentive schemes²⁷ have become an emerging strategy in various PV-related fields and are targeted at a range of HCP (Elovainio, 2010; Gerritsen *et al.*, 2011). From a study done by the Global Health Workforce Alliance²⁸, there are seven characteristics for a good incentive strategy within the healthcare system (Elovainio, 2010). These characteristics include that the incentive scheme has clear objectives, that these are realistic and deliverable, reflect the need needs of the HCP, are well designed, contextually appropriate, fair and transparent, and measurable, and that they include financial and non-financial aspects (Elovainio, 2010). There are five types of incentive schemes that have been identified for the Vigilance System and they will be discussed in the following sub-sections.

Incentives schemes 1: Financial incentives

There are three main categories of financial incentives, namely basic wages and conditions, performance-linked payments, and additional financial services (Weller, 2008; Elovainio, 2010; Gerritsen *et al.*, 2011). The first category ensures that the wages paid are fair when compared to similar roles and responsibilities (Weller, 2008). The second category comprises additional payments or bonuses linked to performance, which are aimed at promoting a culture of ADR reporting within PV systems (Weller, 2008; Gerritsen *et al.*, 2011). The last category,

²⁷ Within the context of this research inquiry, incentive schemes are motivational programs aimed at encouraging stakeholders, such as HCP, to report ADRs within their work environment.

²⁸ <https://www.who.int/workforcealliance/en/>

additional financial services, can refer to fellowships or subsidies for housing, transport and other expenses (Weller, 2008).

Incentives schemes 2: Career and professional development

In the literature, it is argued that HCP value lifelong professional development and learning (Weller, 2008; Gerritsen *et al.*, 2011). Thus, incentives such as access to education programs and training, effective monitoring and supervision can all contribute to a supportive approach to continuous development within the context of PV systems (Gerritsen *et al.*, 2011). Furthermore, by providing educational opportunities, the professional development of stakeholders, such as HCP within the context of ADR reporting, is improved, which further enhances their ability to receive financial and other benefits (Weller, 2008).

Incentives schemes 3: Workload management

In the healthcare landscape, HCP are often burdened by excessive workloads, which subsequently contributes to low motivation, poor performance or ultimately leaving the healthcare profession (Weller, 2008; Elovainio, 2010). Many of these factors that contribute to excessive workloads are a shortage of workers, uneducated staff, or even just an increased demand (Weller, 2008; Elovainio, 2010). Incorporating an incentive of workload management alleviates this challenge to some extent (Weller, 2008). Firstly, overtime payments for staff could be incorporated as a compensation for working overtime and a motivation for employers to improve workload management (Weller, 2008). Secondly, additional leave or time-in-lieu could be introduced to prevent burnout (Weller, 2008). Another possible method is to revise existing roles and responsibilities to improve workload distribution among staff members. Finally, the number of continuous working hours worked by staff members should be regulated to ensure patient safety (Weller, 2008; Elovainio, 2010).

Incentives schemes 4: Positive working environment

Ensuring a positive working environment²⁹ by creating a positive organisational culture and safe working environment is crucial for retaining staff members and improving job satisfaction (Weller, 2008; Elovainio, 2010). Factors to consider incorporating when addressing positive work environments are: supportive management relations, flexible working hours, and systematic communication between management and staff (Weller, 2008; Elovainio, 2010). These may enhance the working environment and may also improve staff member morale (Weller, 2008).

Policy and guidelines

For a system to be effective, it is necessary to have a policy that stipulates a high-level statement regarding the responsibilities of the different stakeholders within the context of PV systems (Mehta, Allen, *et al.*, 2014). Thus, when considering addressing the component of responsibility and accountability within a Vigilance System, a policy should be drafted that ensures that the different stakeholders are clear about the different roles, responsibilities and required tasks within the PV systems (European Medicines Agency, 2017). Such a policy

²⁹ A positive work environment means that stakeholders, within this context of this research inquiry the HCP, are satisfied and content with the relationships, organisational cultures and development within the work environment.

needs to state the required actions called for by the different stakeholders, from PV regulatory bodies to HCP and pharmaceutical manufacturers, and be linked to the different standards, procedures and guidelines relating to PV (WHO, 2004; Mehta, Allen, *et al.*, 2014). The WHO has in fact set up a policy for PV systems that can be used as a guideline on how to address stakeholders' responsibility and accountability within the context of a policy (Chakrabarty and Thawani, 2011).

5.3.10 Component 10: Novel technologies

In the modern-day health landscape, especially given the Fourth Industrial Revolution³⁰, artificial intelligence is becoming part of everyday systems and operations (Yoon, 2017). Thus, for the Vigilance System to be both agile and robust within this context, novel technologies should be investigated and incorporated into the system where appropriate.

5.3.10.1 Intervention identified for component 10: Novel technologies

The four novel technologies identified as relevant to the context of Vigilance System are: (i) blockchain, (ii) datamining, (iii) machine learning and deep learning, and (iv) social media.

Blockchain

Blockchain, commonly used in cryptocurrencies, is a form of distributing data, thus allowing users to process data through nodes on a network instead of through a central authority (IoTCoreSoft, 2018; Price, 2018). Blockchain can be a valuable method of ensuring that data is not falsified or manipulated within the context of PV. Blockchain also provides a reliable flow of data between the different stakeholders, which assists with PDR of ADRs (Price, 2018). Furthermore, the literature also argues that blockchain could be used to improve data integrity, which would assist with ensuring quality management of a PV system (Price, 2018).

Datamining

Due to the growing development of large electronic health data storage systems and advances in technology, the demand for datamining within the healthcare environment has increased significantly (Wilson, Thabane and Holbrook, 2004). Datamining, for the purpose of this study, refers to the utilisation of statistical techniques within the knowledge discovery process, which refers to the extraction process of valid, previously unknown information from large databases (Wilson, Thabane and Holbrook, 2004). Using datamining techniques, data related to ADRs can be identified from medical databases that can be used to build a big-data platform³¹. Then using this platform and different intelligent data processing techniques (keyword auto-mining and image recognition, for instance), an ADR monitoring and filtering model can be developed to assist with the identification of suspected ADRs (Wu *et al.*, 2017).

Machine learning and deep learning

Machine learning is an application that offers a system the ability to automatically deduce and gain insights from past experiences in order to improve a system automatically (Price, 2018; Lee and Chen, 2019). Conventional machine learning methods have been used to keep track

³⁰ The fourth industrial revolution refers to environment in which disruptive technologies are fundamentally changing the operations of current work practices by increasing productivity (Yoon, 2017).

³¹ Within the context of this research inquiry, a big-data platform is a universal data storage server that be utilized to access information related to reported ADRs.

of post-marketing drug side effects, however the complex biological and chemical structures of drugs often make it more challenging to be detected and thus deep learning methods are often preferred for prediction tasks (Lee and Chen, 2019). In a study done by Lee (2019), a two-stage framework was developed based on using deep learning methods to predict the association between ADRs and drugs; it involved integrating individuals' biological data into a system. This framework can be used to determine the likelihood of an ADR occurring in a patient before a new medication is prescribed (Lee and Chen, 2019).

Social media

Social media generates large volumes of data that can be utilised for signal and ADR detection, and thus assist with the challenge of under-reporting within a PV system (Nikfarjam *et al.*, 2015; Sloane, Osanlou and Lewis, 2015). The use of social media sites as platforms to facilitate discussions of ADRs between patients and HCP have become increasingly predominant (Nikfarjam *et al.*, 2015). Furthermore, suspected ADRs can also be identified from social media and recorded for data gathering (Nikfarjam *et al.*, 2015; Sloane, Osanlou and Lewis, 2015). There are however still technical and ethical challenges (i.e. the use of informal language on social media platforms, for instance, and considerations of privacy and confidentiality) that have to be addressed for this to become a viable intervention (Nikfarjam *et al.*, 2015). Furthermore, effective techniques, such as algorithms that can be used to identify ADRs through social media platforms, are still in the process of development (Nikfarjam *et al.*, 2015; Sloane, Osanlou and Lewis, 2015). However, the use of social media brings with it the opportunity for early detection and enhancement of patient safety (Sloane, Osanlou and Lewis, 2015).

5.4 CHAPTER 5 CONCLUSION

In this chapter, the third phase in the systems engineering process, namely the functional analysis, was conducted with the aim of identifying intervention strategies that would address the requirements specification, which led to the proposition of the Vigilance System - an context-specific PV system for MPP drug provision systems aimed to assist with the effective and efficient reporting of ADRs within this context. Building on the insights gained from the contextualisation of the identified intervention strategies, an index, the Vigilance System Component-Intervention Index, was developed to provide an overview of the various components and intervention strategies to address when considering the implementation of a Vigilance System

Building on the insights gained from this chapter, in the following chapter the final phase of the systems engineering approach will be taken, namely, the design synthesis. The aim of this phase is to transform the Vigilance System Component-Intervention Index into an operational tool that will assist with the implementation of the Vigilance System.

Chapter 6: Decision support tool development

In this chapter, the final phase of the systems engineering approach, the design synthesis, is conducted; the design synthesis entails the development of a functioning product based on the findings from the previous phase, in this case, the functional analysis conducted in Chapter 5 (United States Government, 2001). In the context of this research study, the design synthesis is the development of a decision support tool, by synthesising the findings of the functional analysis, i.e. the Vigilance System Component-Intervention Index that was documented in Chapter 5. The purpose of the decision support tool is to facilitate the development of an implementation strategy for a Vigilance System within the context of the MPP drug provision systems that addresses the three specific diseases (i.e. HIV, TB and Hepatitis C), within RLS.

The design synthesis phase is divided into two sub-phases: sub-phase A relates to the development of a decision support tool, and sub-phase B relates to the validation of the developed tool. Sub-phase B is presented and discussed in Chapter 7.

In this chapter, the tool development, the different dimensions of the tool, and the implementation of the tool are discussed. Figure 6.1 shows how the design synthesis relates to the overarching systems engineering approach that was followed in this research study.

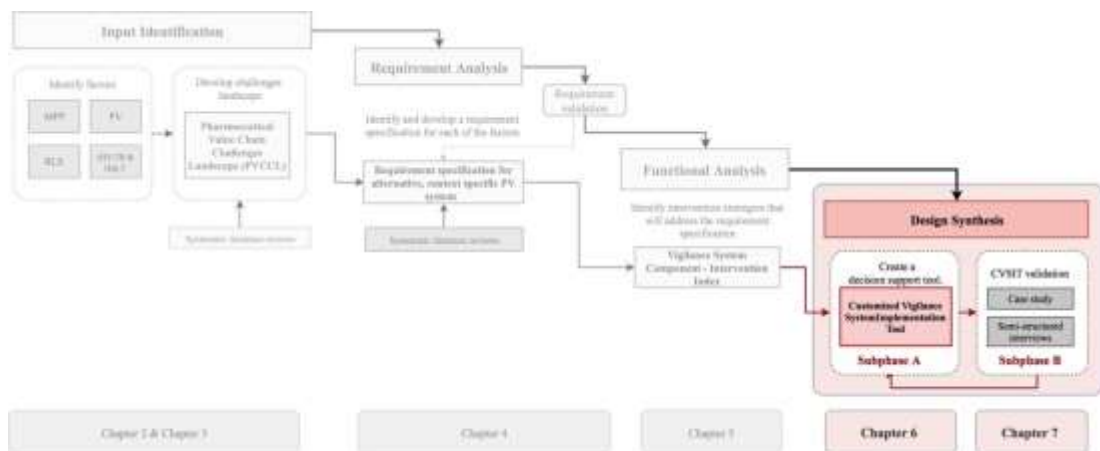


Figure 6.1: Systems engineering approach: Design synthesis: Subphase A

6.1 DECISION SUPPORT TOOL PURPOSE, DEVELOPMENT APPROACH, AND OVERVIEW

The design synthesis phase is the final phase of the systems engineering approach and draws together the findings from the preceding phases, i.e., (i) input identification, (ii) requirement analysis, and (iii) functional analysis. The design synthesis phase is the process of defining and developing a functioning product that can be implemented to address the research problem (United States Government, 2001). During this research inquiry, it was found that PV systems in the environment of MPP drug provision systems are not adequately designed to address the unique needs or challenges faced in this environment. Thus, this research was aimed at

developing a decision support tool that would assist with the implementation of a, context-specific PV system (i.e. a Vigilance System) within the context of the MPP.

In this section, the purpose of the tool, an overview of the tool and the approach used to develop said tool will be discussed.

6.1.1 Decision support tool purpose

In order to synthesise the operability of the Vigilance System Component – Intervention Index, which provides a overview of the different components that should be addressed when implementing a Vigilance System, a decision support tool referred to as the *Customised Vigilance System Implementation Tool (CVSIT)* was developed. The CVSIT is a decision support tool that assesses a drug projects' profile, with respect to the specific drug being considered, together with the environment and resource availability, in order to developing a *customised* implementation strategy for a Vigilance System. This customised implementation strategy provides an approach of how to address the implementation of a Vigilance System, by identifying which of the intervention strategies, as provided for in the Vigilance System Component-Intervention Index, are most appropriate to the specific drug provision project under consideration. Furthermore, when considering this implementation strategy, it should be noted that this approach provides an overview of the intervention strategies most appropriate or suitable for a specific project, given the context-specific characteristics of the project, and subsequent to the identification of such intervention strategies, should the financial, technical and operational feasibility be pursued.

6.1.2 Decision support tool development approach

The CVSIT was developed based on the insights gained form the Vigilance System Component-Intervention Index with reference to the 10 Vigilance System components and their subsequent intervention strategies. In order for the tool to facilitate the process to determine the intervention strategies most appropriate for the specific project under consideration, a set of inclusion/exclusion criteria set was established for each of the interventions, that stipulate the requirements called for by the specific intervention in order to operate effectively within the context of the specific drug provision project, given the environment of the MPP drug provision systems. These inclusion/exclusion criteria sets were developed based on the findings of the Vigilance System Component-Intervention Index and the associated literature. Furthermore, these inclusion/exclusion criteria sets are related to the requirements that a specific intervention strategy would call for when considering the environment in which the drug provision project would operate, i.e. the available resources, the accessible healthcare and reporting facilities, as well as the characteristics of the project, i.e. the specific drug being considered and the targeted audience. A detailed explanation of these criteria sets for the different intervention strategies can be found in Appendix F, Section F.1.

From the above-mentioned sets of criteria, four project profile dimensions, which facilitate the gathering of the respective data that is required to determine which of the intervention strategies would be most appropriate for the specific drug provision project under consideration. In the following sub-section, an overview will be given of the tool and its different dimensions.

6.1.3 Decision support tool overview

The CVSIT is a Microsoft Excel³² based tool that consists of four dimensions, i.e. Dimension 1– vigilance profile assessment, Dimension 2 – Vigilance System Component-Intervention Index, Dimension 3 – profile-interventions mapping tool, and Dimension 4 – vigilance implementation strategy. These dimensions and how they are combined to form the CVSIT are shown in Figure 6.2. Dimension 1 is the input section of the tool and is found at the user interface level, as the user is required to provide the input data. Dimensions 2 and 3 are the background logic level of the tool, and Dimension 4 is the user output level.

The first dimension is the *vigilance profile assessment* dimension and is aimed at determining and assessing the profile of the project, by collecting the required data with respect to the characteristics and environment. There are four domains that have to be considered in order to gather all the necessary data to create a *vigilance profile*, which is the output of Dimension 1, for the project under consideration. These four domains were identified by drawing on the inclusion/exclusion criteria set of the intervention strategies as discussed in Section 6.1.2. As mentioned, this dimension is at the user interface level and thus requires the input from the user. The user is required to complete questions related to each of the domains in order to gather all the required data.

The second dimension is the Vigilance System Component-Intervention Index which was developed in Chapter 5. This dimension provides the information on the 10 vigilance components with their respective implementation strategies.

The third dimension is the *profile-interventions mapping tool* dimension. And, in this dimension the project's unique vigilance profile, as developed in Dimension 1, is mapped against the Vigilance System Component-Intervention Index to identify which of the intervention strategies would be most appropriate or suitable for the drug provision project under consideration. This domain is the background logic section of the tool and is not accessible by the user. The background logic associated with the *Profile-intervention mapping tool* is discussed in detail in Section 6.2.3. The input to this dimension, as shown in Figure 6.2, is the output from the first dimension (i.e. the vigilance profile of the project) and the output of the second dimension (i.e. the information related to the vigilance components with their respective implementation strategies). The output from this dimension is found in Dimension 4.

The fourth and final dimension, which is the output of Dimension 3, is the vigilance implementation strategy, which provides the user with a customised strategy for the implementation of a Vigilance System. This provides the user with the identified intervention strategies that are most appropriate to the project under consideration, given the context. As mentioned above, the financial, technical and operational feasibility of interventions fall outside of the scope of the CVSIT. Each of these dimensions of the CVSIT is discussed in detail in the following sections.

³² Microsoft Excel is a software product delivered by Microsoft office that has the potential to develop relatively sophisticated scientific computation programmes using programming capabilities (Melendez, 2018).

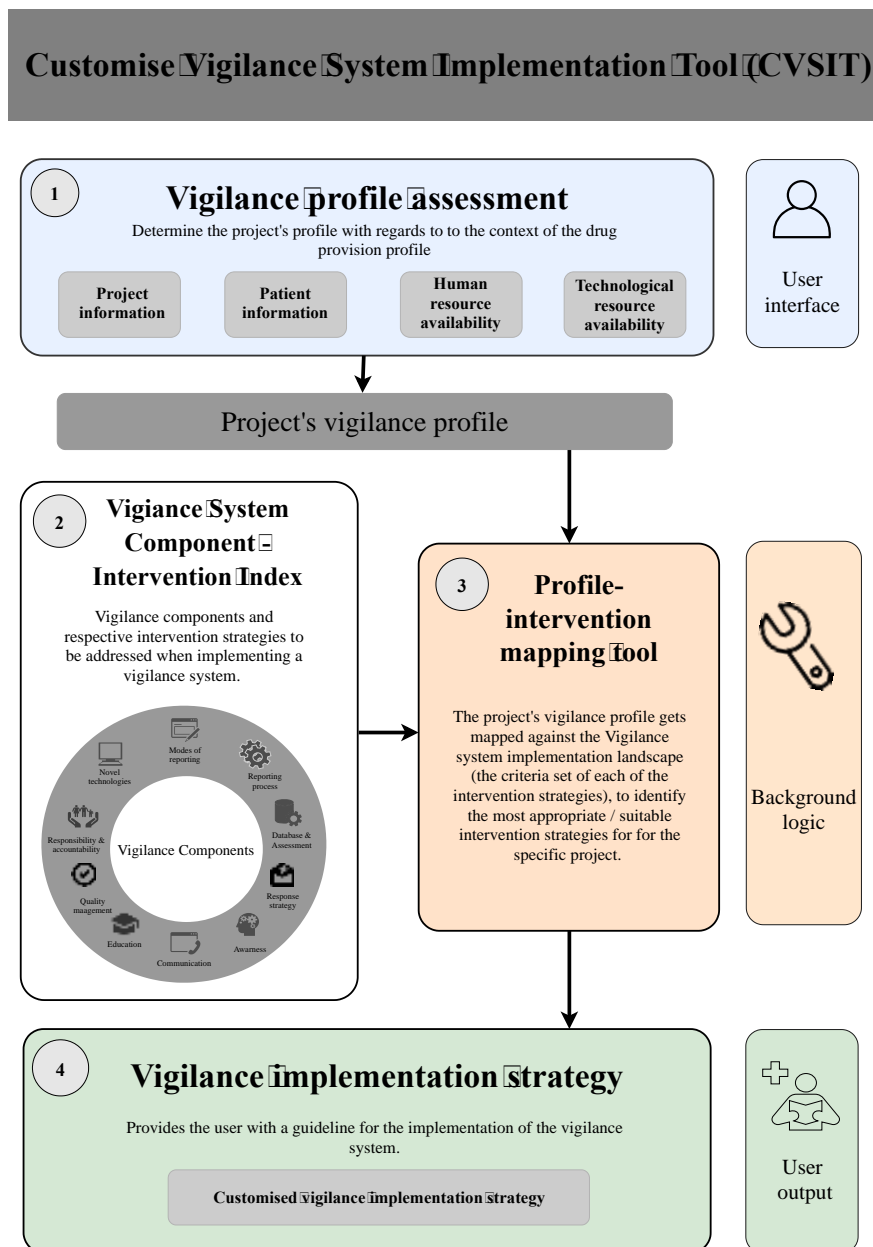


Figure 6.2: Graphical representation of the CVSIT

6.2 THE CUSTOMISED VIGILANCE SYSTEM IMPLEMENTATION TOOL

In this section a detailed discussion of each of the dimensions, as briefly discussed in Section 6.1, will be provided.

6.2.1 Dimension 1: The vigilance profile assessment

This dimension is aimed at determining the project's vigilance profile with regard to the implementation of a Vigilance System best fit for the specific project. This dimension is situated in the user interface and requires the user to answer different questions with respect to the four domains, in order for the tool to gain all the required data with respect to the specific project, the targeted patient group(s), and the availability of both human and technological resources, as depicted in Figure 6.3. These four domains are individually assessed in the Excel spreadsheet, which requires the input from the user. For this dimension, the CVSIT has four

Excel based forms, one for each domain that is developed to capture the necessary information from the user to ensure that the implementation strategies that best fit the project can be identified in the third dimension. The four respective Excel sheets, corresponding to the four domains of the Vigilance profile assessment dimension, are shown in Appendix F, Section F.2.1.

Once the profile data has been captured, a vigilance profile for the respective project is developed, which is then transferred to Dimension 3 – the profile-intervention mapping tool. An overview of the four domains is given below.

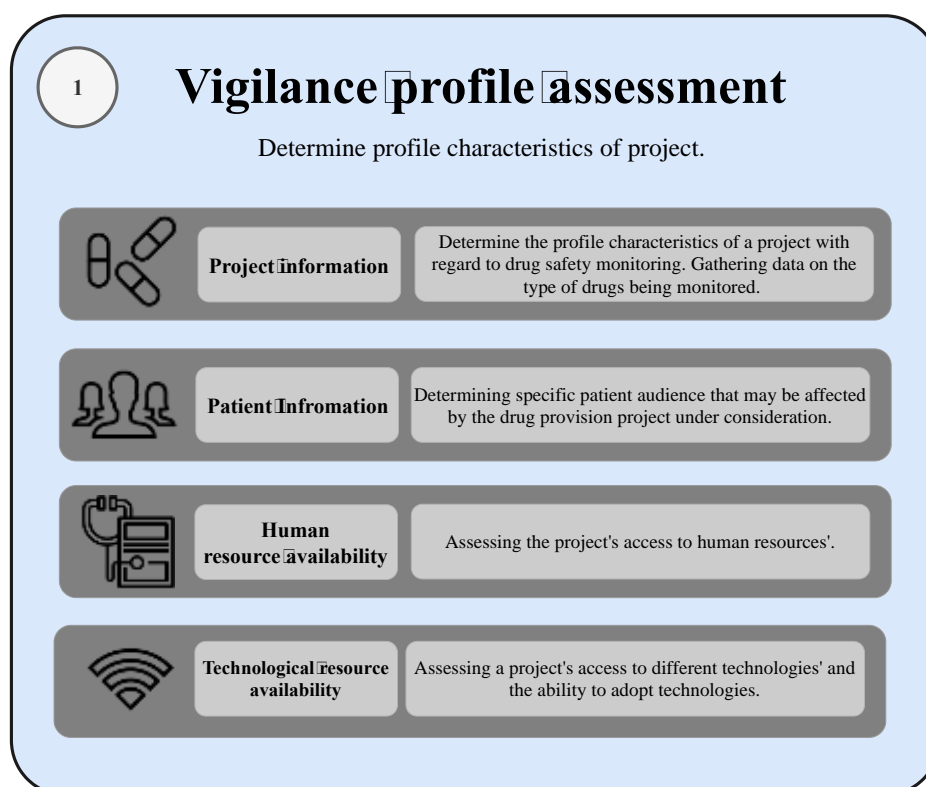


Figure 6.3: Dimension 1 - Vigilance profile assessment

6.2.1.1 Domain 1: Project information

The project information domain is aimed at capturing data with regard to the focus of the project's aim for the Vigilance System, such as: (i) data on the drugs being considered in the project, (ii) considerations in respect of ADRs that have to be monitored and (iii) the healthcare facilities being considered for the project. This domain corresponds to the first Excel based form of the CVIST, and is found in Appendix F, Section F.2.1, Figure F.1.

6.2.1.2 Domain 2: Patient profile

In this domain, the specific patient audience that may be affected by the drug provision project under consideration, is determined and assessed. The specific factors of the patient audience that need to be considered when identifying the applicable intervention strategies of the project are determined, whether or not the project focuses on a controlled group is considered, the education level of the patient audience with regard to drug safety monitoring is evaluated, and the ability of the patient audience to report ADRs without visiting healthcare facilities is

reflected on. The Excel based form for the patient profile domain is shown in Appendix F, Section F2.1, Figure F.2.

6.2.1.3 Domain 3 : Human resource availability

In this domain, the extent to which the project has access to human resources, i.e. HCP such as doctors, pharmacist or other specific resources, who can assist with ADR reporting are considered. It also considers the availability and the education level of the HCP with regard to drug safety monitoring. The Excel based form for the human resource availability domain is shown in Appendix F, Section F2.1, Figure F.3.

6.2.1.4 Domain 4 : Technological resource availability

This domain determines the project's access to different technologies, and thus determines whether a project has access to different technologies, such as the internet, handheld devices, and/or desktops for the purpose of ADR reporting and monitoring. It also determines the capacity of the drug provision project to investigate and adopt novel technologies, such as blockchain, datamining, machine learning or social media, to assist with ADR detection. This domain is aimed at capturing information to determine if the project will be able to utilise technology focused intervention strategies when implementing the Vigilance System. The Excel based form for the *technological resource* availability domain is shown in Appendix F, Section F2.1, Figure F.4.

6.2.2 Dimension 2: Vigilance System Component–Intervention Index

The second dimension of the CVSIT tool is the *Vigilance System Component-Intervention Index*, which was developed in Chapter 5. This index provides an overview of the different Vigilance System components that have to be addressed when developing a Vigilance System. For reference purposes, the key features are reiterated here: Each of the Vigilance System components have a subsequent set of intervention strategies that could be implemented to address the specific component. The index contains 10 different Vigilance System components, which are grouped into three categories, namely: (i) direct components and interventions, (ii) supporting components and interventions, and (iii) additional factors. The direct components refer to the components that directly affect the ADR reporting process, the supporting components refer to those that address the effectiveness of a Vigilance System within the context of the profile of the drug provision project, and the additional factors are the components that are neither direct nor supporting components but that rather consider the drug provision project from a future perspective. The different components are illustrated in Figure 6.4. Furthermore, this dimension only includes the inclusion/exclusion criteria for the different intervention strategies, as discussed in Section 6.1.2 and found in Appendix F, Section F.1.

Similar to the project vigilance profile, the Vigilance System Component–Intervention Index data is transferred to Dimension 3 (i.e. the Excel based form for the third dimension), viz., the *profile-intervention mapping*, where the different intervention strategies are evaluated against the project's vigilance profile to determine which of the intervention strategies are most applicable and suitable for the specific project. The Excel based form for the *second* domain is shown in Appendix F, Section F2.2.

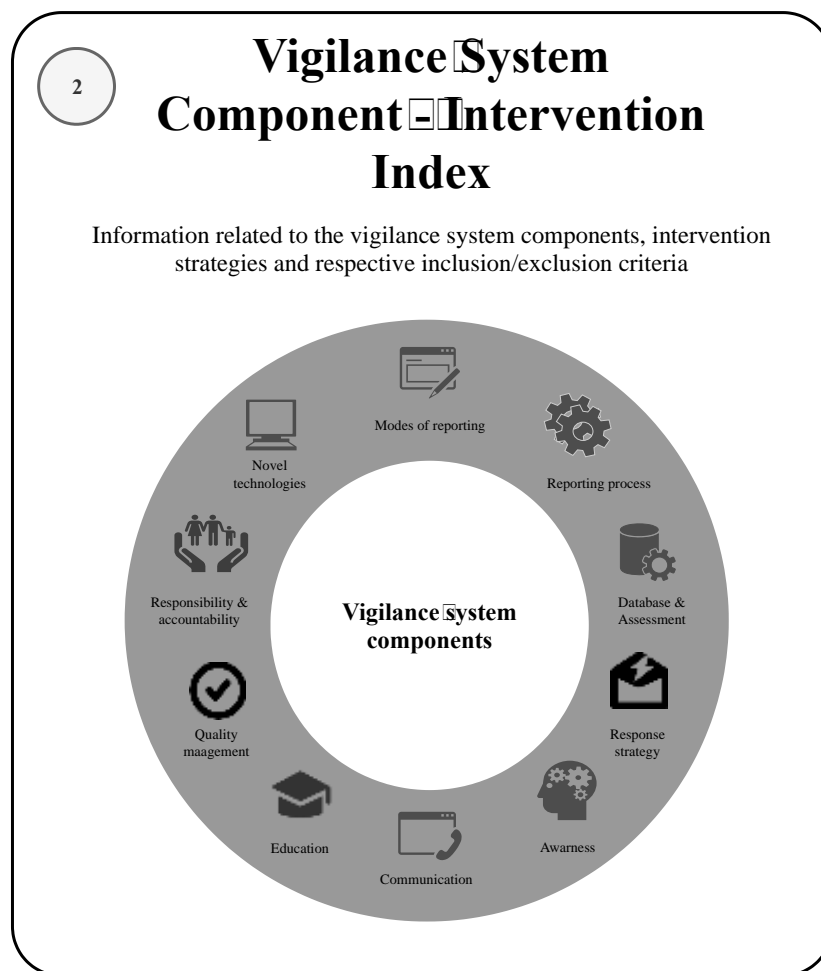


Figure 6.4: Dimension 2 - Vigilance System Component-Intervention Index

6.2.3 Dimension 3: Profile-intervention mapping tool

The third dimension of the CVSIT tool, see Figure 6.5, the *profile-intervention mapping*, is the background logic section of the Excel based tool. In this dimension, the output of the first dimension, i.e. the project vigilance profile, and the second dimension information, i.e. the vigilance components, intervention strategies and respective inclusion/exclusion criteria sets, are mapped against each other to determine which of the intervention strategies are most appropriate or suitable to the specific drug provision project, based on the information gathered with reference to the project's profile.

As mentioned, each of the intervention strategies, as shown in the Vigilance System Component – Intervention Index, have a specific set of inclusion/exclusion criteria, based on the requirements called for by the intervention strategies in order to operate effectively in a Vigilance System within the environment of the drug provision project (shown in Appendix F). As mentioned, these criteria sets were based on the findings of the Vigilance System Component – Intervention Index and the related literature as documented in Chapter 5. These sets of criteria, along with the project vigilance profile data, are mapped using Visual Basic of Applications (VBA) programming in Excel to determine which of the intervention strategies would be the most appropriate or suitable to the specific project. Furthermore, the profile-

intervention mapping tool also determines if the project's profile calls for additional aspects of ADR reporting to be considered when implementing certain intervention strategies, such as the type of information that needs to be captured for the specific project's ADR report. The Excel based form for the 3 dimension is shown in Appendix F, Section F.2.3, while the background logic is shown in Section F.3.

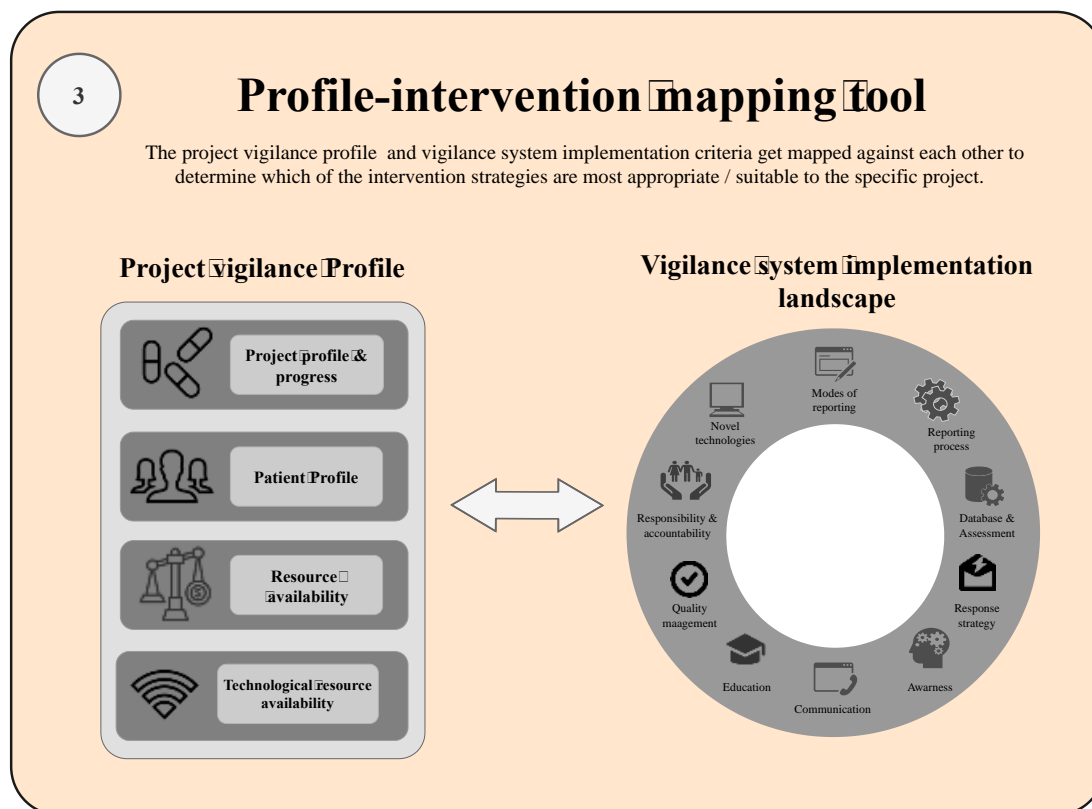


Figure 6.5: Dimension 3 - Potential mapping assessor

6.2.4 Dimension 4: Vigilance implementation strategy

The final dimension of the CVSIT tool is the *Vigilance implementation strategy dimension*, see Figure 6.6. This yields the customised vigilance implementation strategy for the specific drug provision project under consideration. Its objective is to provide the user with an implementation strategy for a Vigilance System, i.e. the different vigilance components, which need to be addressed with their respective implementation strategies that are most suitable or appropriate for the specific drug provision project. In this dimension of the Excel tool, the best suited intervention strategies for each of the vigilance components are provided, with a short description of each. However, they still require additional feasibility investigations to ensure that they would in fact be the most effective implementation strategy for the specific project under consideration. However, this phase lies outside of the scope of the CVSIT. A description of the unfavourable intervention strategies is also provided, in case the user would like to investigate these intervention strategies as well. Furthermore, the customised vigilance implementation strategy also provides the user with additional important information to consider, based on the project's vigilance profile, the ADR reports, the specific patient groups, and the education interventions. The Excel based form for the fourth dimension is shown in Appendix F, Section F.4.

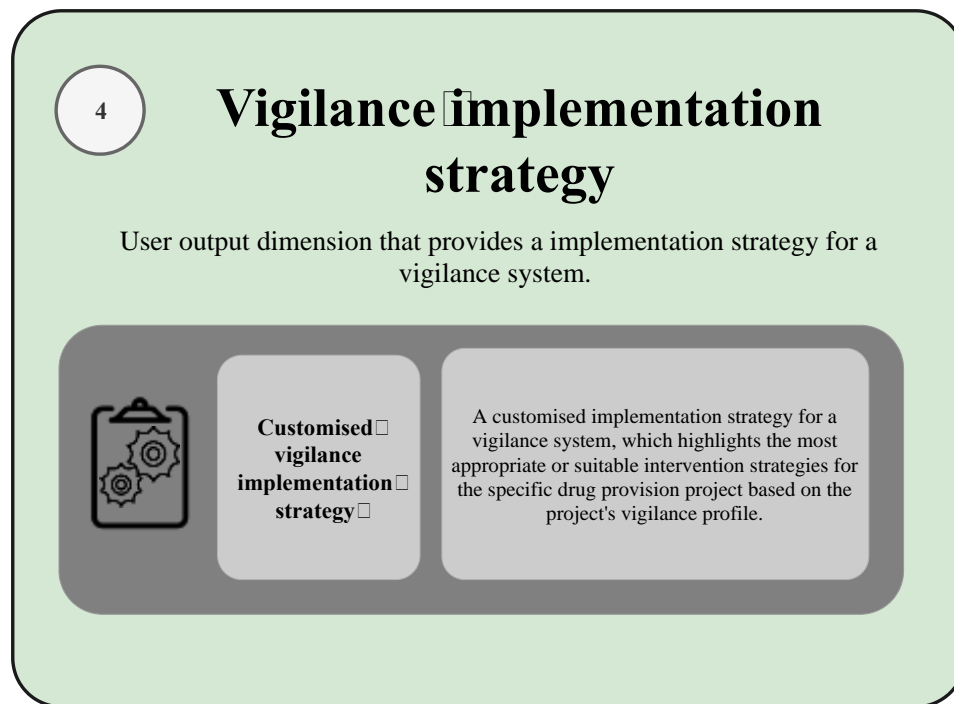


Figure 6.6: Dimension 4: Vigilance implementation strategy

6.3 OPERATIONALISATION OF THE CUSTOMISED VIGILANCE SYSTEM IMPLEMENTATION TOOL

In this section, the operationalisation of the CVSIT tool is discussed, i.e. how the different dimensions of the tool can or should be implemented, the flow of data and information through the CVSIT and between the various dimensions and domains, and the background logic of the CVSIT.

The CVSIT may be used for two distinct, yet related objectives, and can be denoted based on the ‘direction’ in which the tool is operationalised – see Figure 6.7. The two different operationalisation paths each serve a different outcome or objective with regard to the development of a vigilance implementation strategy. The two operationalisation paths are: (i) *CVSIT Operationalisation Path 1: Project profile to vigilance implementation strategy guide*, and *CVSIT Operationalisation Path 2: Vigilance implementation strategy to project profile guide*.

In Path 1, the CVSIT may be used to assess a specific drug provision project’s profile and to identify applicable intervention strategies for a Vigilance System related to the project. Essentially this is the operationalisation path that is aligned with how the CVSIT is described in Section 6.1.3 and Section 6.2 – thus progressing through Dimensions 1 to 4. However, during the development of the CVSIT, it became evident that it may also be used in the form of an index guide, which provides the user with the considerations that a specific intervention strategy calls for, thus operationalising the CVSIT through Dimensions 4 to 1 (see Figure 6.7). Path 1 is referred to as the *CVSIT project profile to vigilance implementation strategy guide*, as it provides the user with an implementation strategy for a Vigilance System and, as mentioned, because it operationalises the CVSIT from Dimension 1 through to Dimension 4. Path 2, the *CVSIT vigilance implementation strategy to project profile guide*, provides the user with specific considerations with respect to the characteristics of the project, the targeted

audience group, and the accessibility to human and/or technology resources, which each of the intervention strategies calls for in a Vigilance System.

It is thus suggested to use Path 1 when deciding on a customised implementation strategy for a Vigilance System by identifying which intervention strategies are most appropriate or suitable for the specific drug provision project, based on the profile of the project with respect to the specific drug being considered, the environment and the availability of resources.

It is suggested to use Path 2, in contrast, when a specific intervention strategy should be adopted in the implementation strategy for a Vigilance System, by providing the consideration that said intervention strategy would call for with respect to the profile of the project, i.e. the human resources availability, the technological resources available and the target patient group.

The respective operationalisation paths, their respective purposes, and data flow will be discussed in more detail in the following sections.

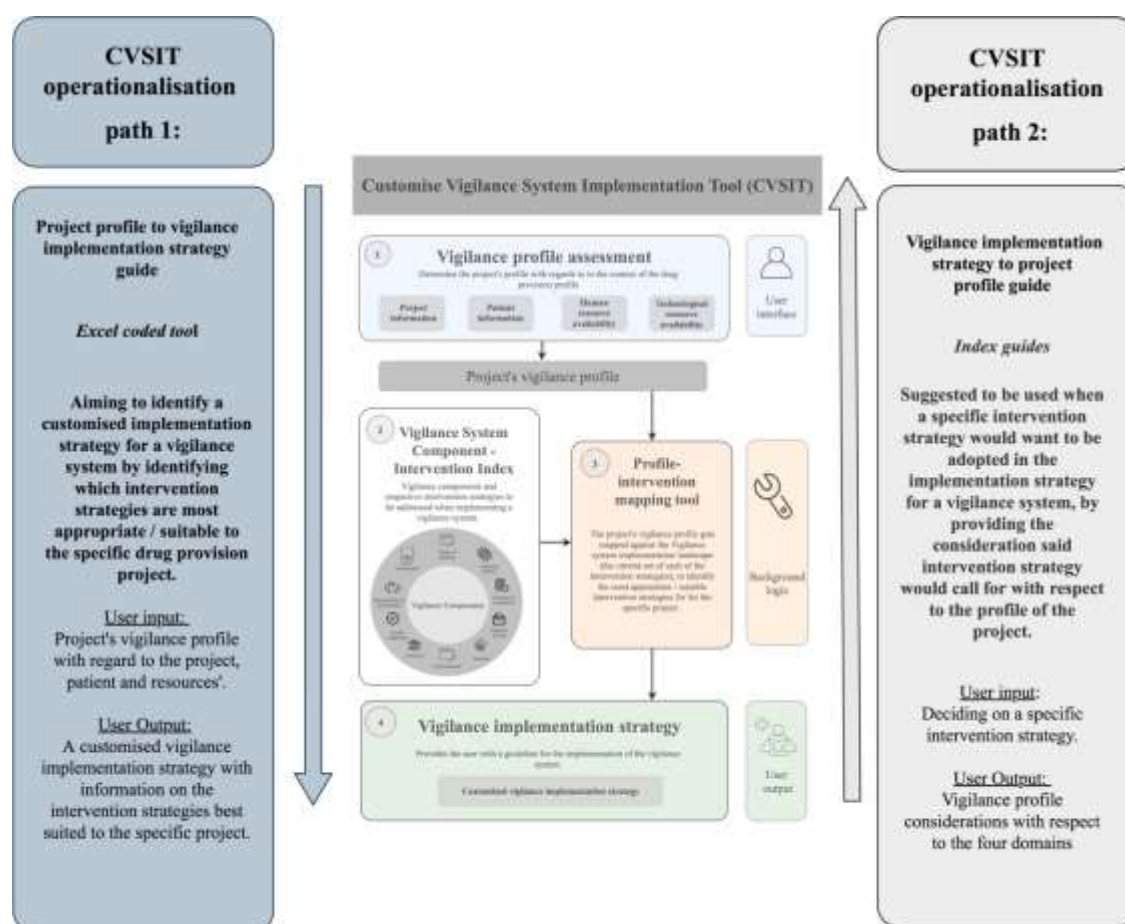


Figure 6.7: Graphical representation of CVSIT operational path 1 and CVSIT operational path 2

6.3.1 Customised Vigilance System Implementation Tool operationalisation path 1: Project profile to vigilance implementation strategy guide

As mentioned, Path 1 of the CVSIT progresses from Dimension 1 through to Dimension 4, with the user providing project profile data related to the specific drug provision project, the patient group that is being focused on, and the availability of resources. The output of this path

is a vigilance implementation strategy customised to the profile of the project under consideration.

The process flow associated with Path 1 is illustrated in Figure 6.8. During the vigilance profile assessment, the user provides project data related to the project information domain, the patient information domain, the human resource availability domain, and the technology resource availability domain. The user is requested to answer questions related to these four domains, after which this data is captured in the Excel based form (see Appendix F, Section F.2.1) and transferred to the profile-intervention mapping tool dimension's Excel based form. The most appropriate or suitable intervention strategies are then indicated to the user in the final dimension. A high-level process map was created to represent the flow of the data (see Figure 6.8), but a more detailed version of the data flow can be found in Appendix F, Section F.3, along with the different dimensions of the CVSIT in Appendix F, Section F.2.

6.3.2 Customised Vigilance System Implementation Tool operationalisation path 2: Vigilance implementation strategy to project profile guide

Path 2 of the CVSIT moves in the opposite direction, i.e., from the strategy to the specific project profile, and is aimed at providing information related to the considerations the intervention strategies call for in a Vigilance System. Path 2 allows the user to select specific intervention strategies that they may want to implement in a Vigilance System, and Path 2 then gives the user the relevant project profile considerations to consider with respect to the environment and the availability of resources. This set of considerations that will support the implementation of the intervention under consideration can then be compared to the existing profile of the drug provision project to identify and highlight any misalignments between the existing profile and the required profile based on the intervention's system considerations. The process flow that depicts Path 2 is shown in Figure 6.9.

Path 2 of CVSIT consists of three index guides: (i) considerations of direct components and interventions, (ii) considerations of supporting components and interventions, and (iii) considerations of additional factors. Each of these index guides give the user a list of the different intervention strategies and the respective considerations that these interventions call for in order to be adopted effectively in a Vigilance System. These considerations are directly linked to the vigilance profile domains, namely (i) project information, (ii) patient information, (iii) human resource availability, and (iv) availability of technology resources.

It is important to note that these considerations are not an exhaustive set of the considerations the intervention strategies need for an effective implementation, but that they are aimed at providing guidance with respect to the context of this tool and the four domains, i.e. the details of the project, the patient, and the human and technology resources. There may be other considerations that fall outside these four domains, such as feasibility, and technical or financial considerations.

The three index guides, shown in Figure 6.10 to Figure 6.12, are subdivided into the three categories with respect to the Vigilance System Component – Intervention Index, i.e. the direct, supporting and additional factors. The first index guide (*considerations of direct components and interventions*) lists the four direct Vigilance System components, namely, (i) the mode of reporting, (ii) the reporting process, (iii) the response strategy, and (iv) the database and the associated intervention strategies along with the considerations each

intervention strategy calls for in a Vigilance System. The second index guide (*considerations of supporting components and interventions*) has a similar format, but with regard to the supporting vigilance components, i.e., (i) awareness, (ii) communication, (iii) education, (iv) quality management, and (v) responsibility and accountability. Lastly, the third index guide (*considerations of additional factors*) has a similar format but within the context of novel technologies.

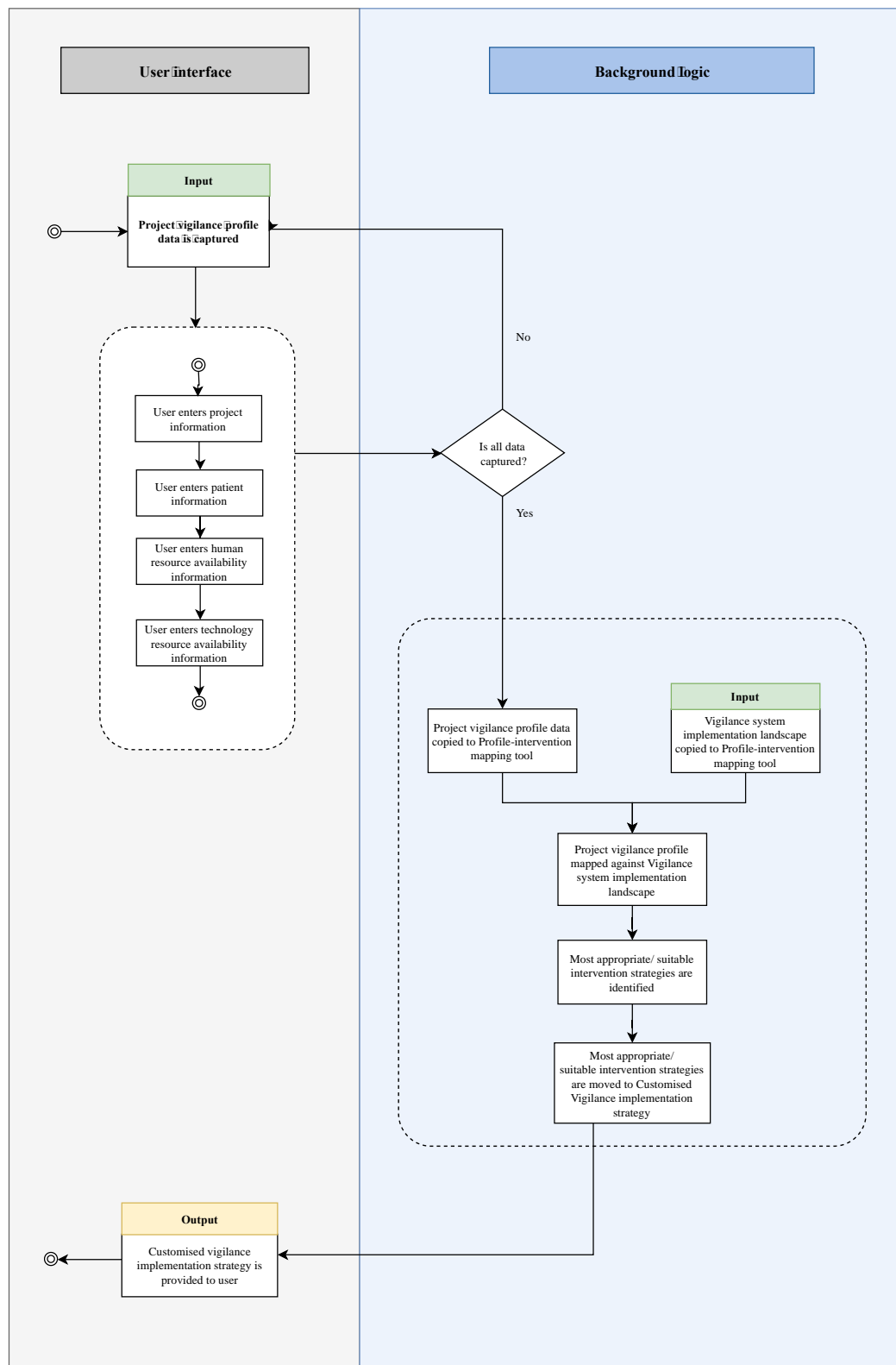


Figure 6.8: High level process map for CVSIT operational path 1

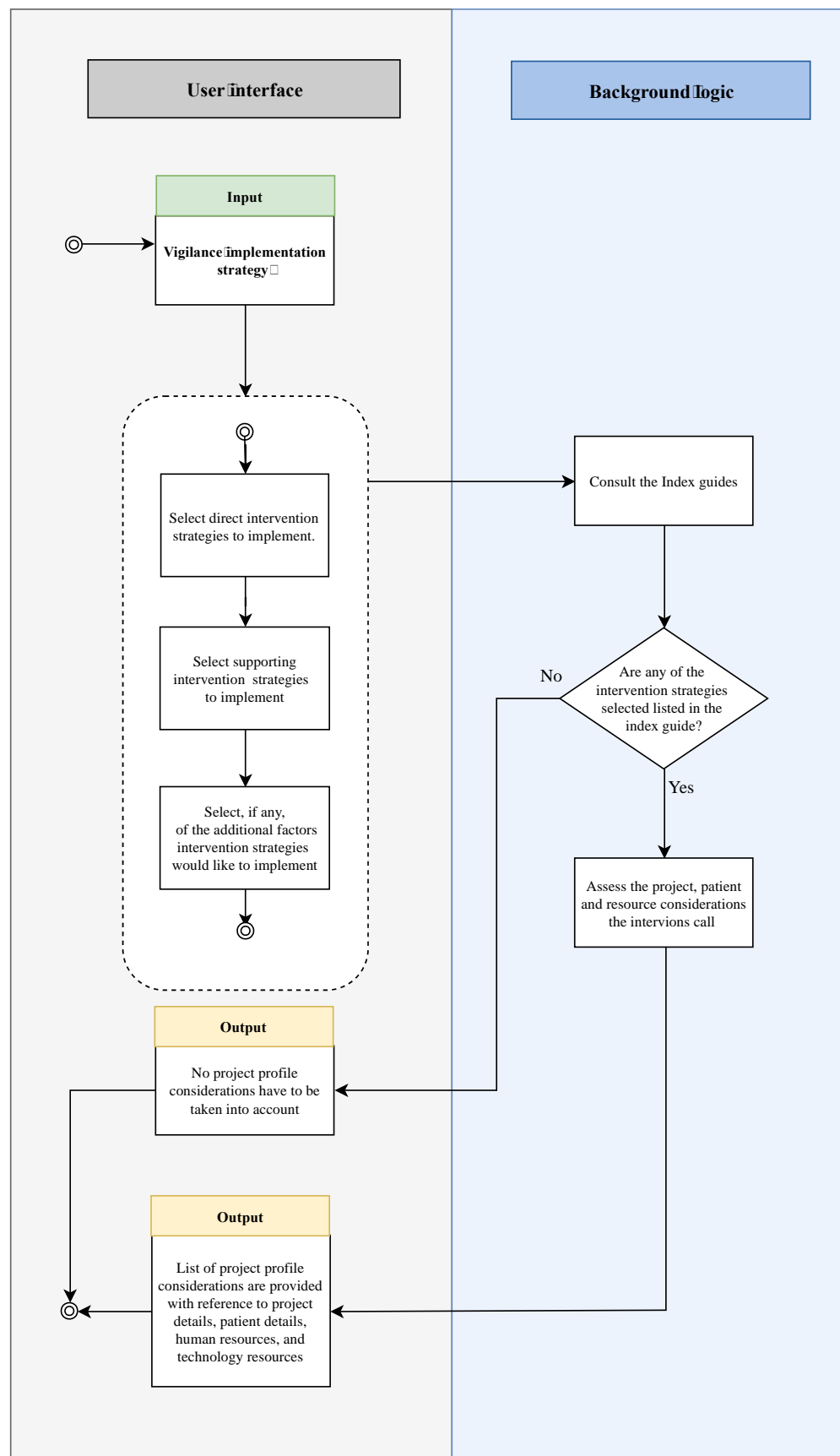


Figure 6.9: High level process map for CVSIT operational path 2

Direct components & interventions considerations

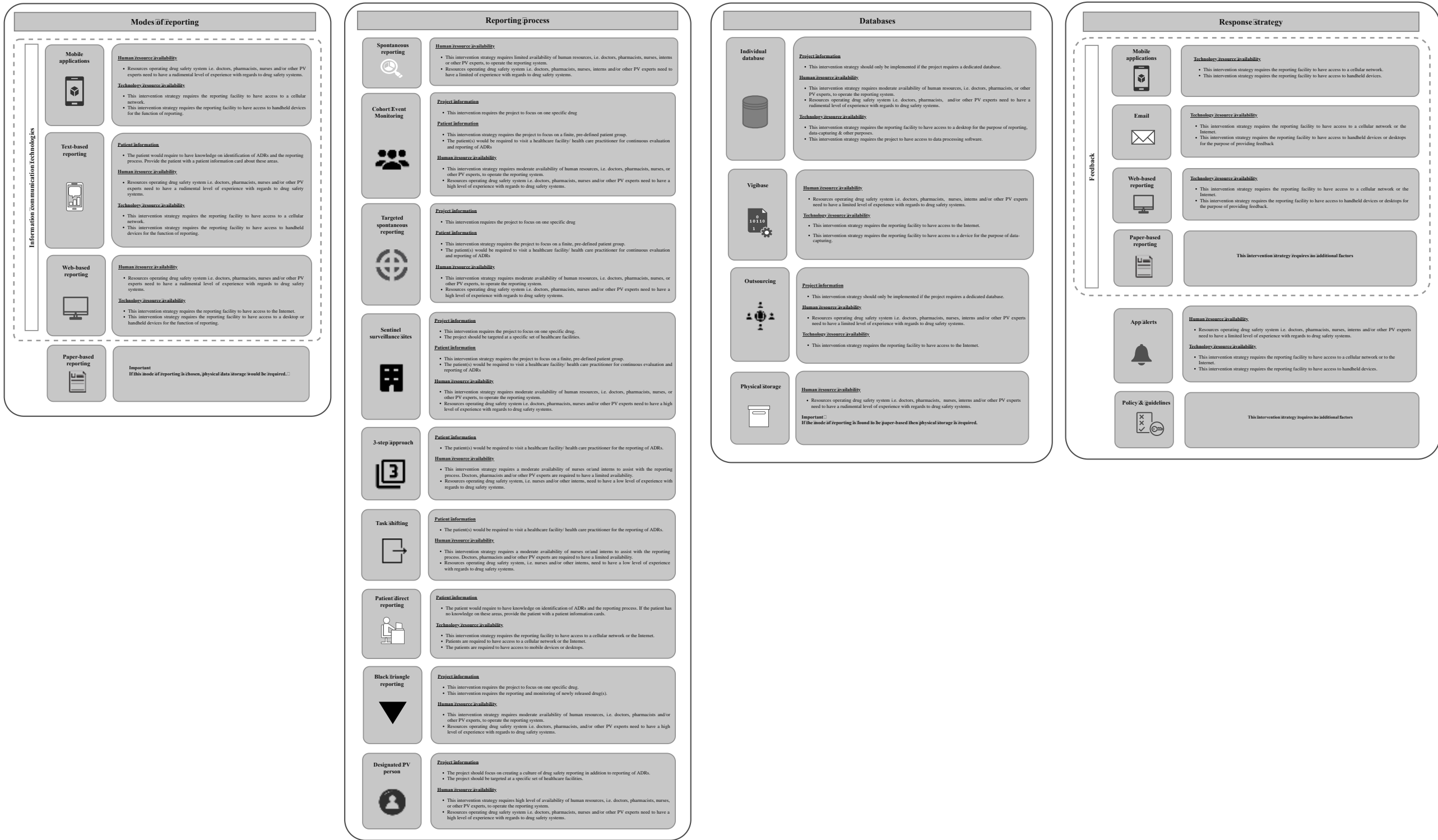


Figure 6.10: Index guide for consideration of direct components and interventions

Supporting components & intervention considerations

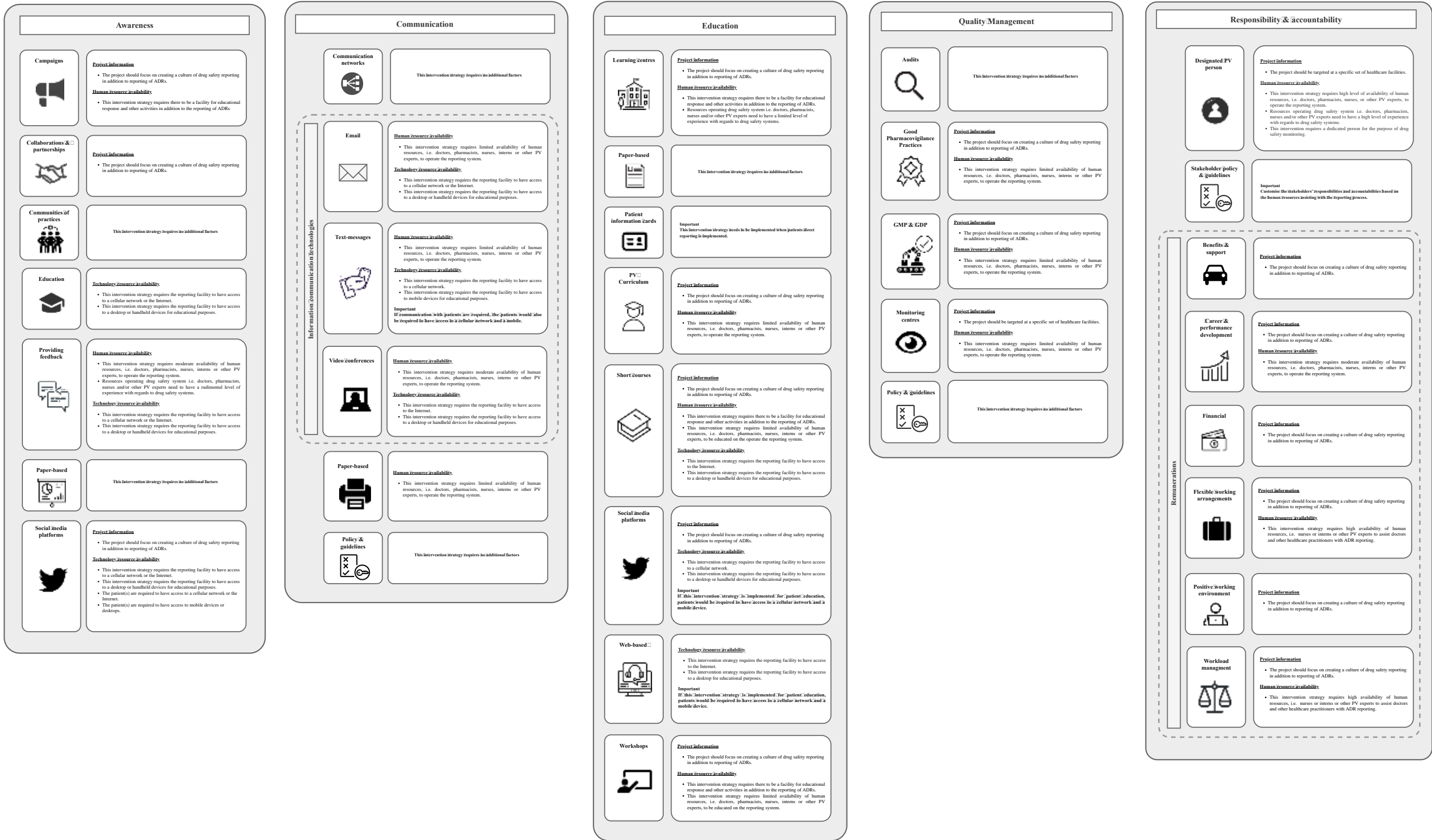


Figure 6.11: Index guide for consideration of supporting components and interventions

Additional factors considerations

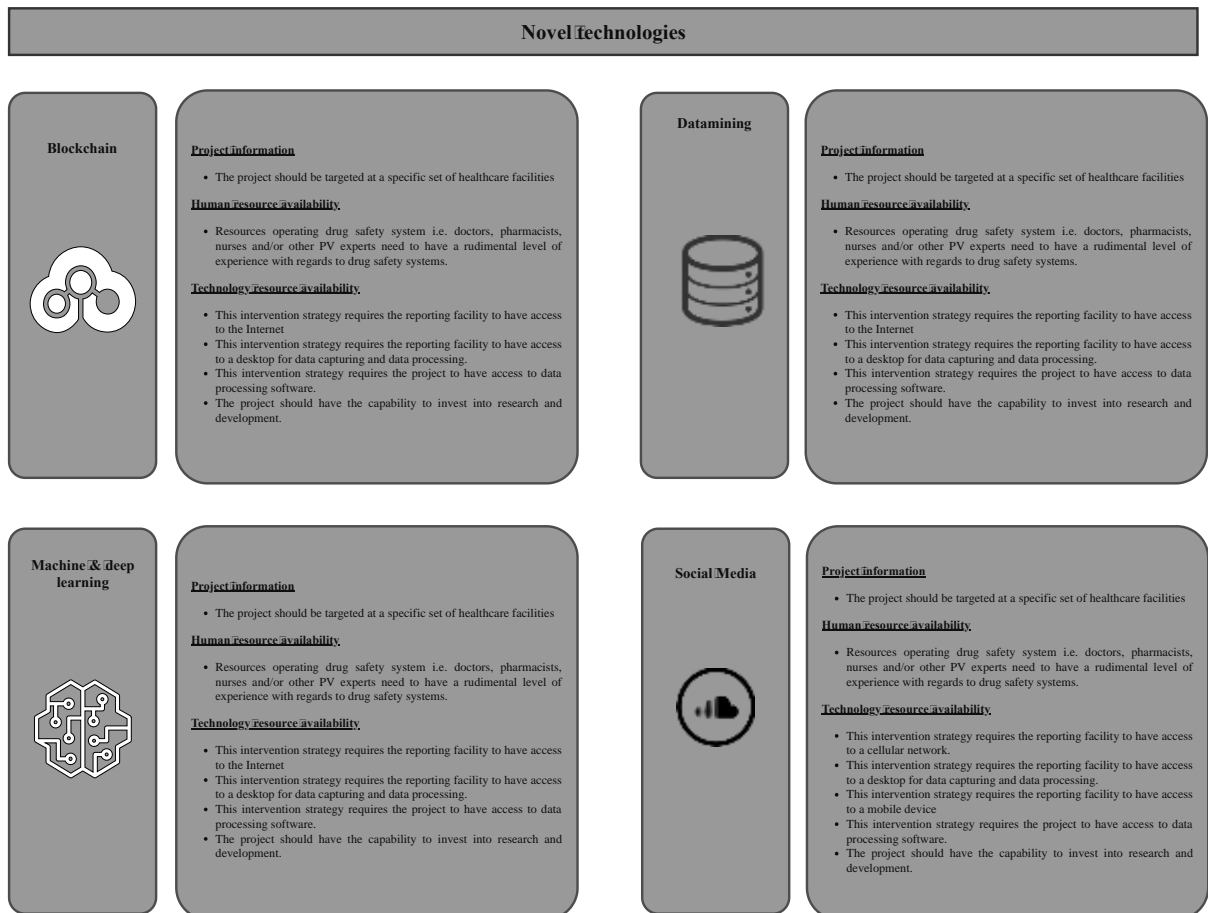


Figure 6.12: Index guide for additional factors considerations

6.4 CHAPTER 6 CONCLUSION

In this chapter, sub-phase A of the final phase of the systems engineering approach, namely the design synthesis, was conducted with the aim of developing a decision support tool, that synthesises the operability of the Vigilance System implementation landscape.

The aim of this tool is to assist drug provision projects in the environment of the MPP drug provision systems with the implementation of a Vigilance System that would facilitate the effective and efficient reporting of ADRs within this context. CVSIT was developed in order to assess a project's profile with respect to the specific drug being considered, the particular environment and the availability of resources, with the aim of customising an implementation strategy for a Vigilance System by identifying the intervention strategies most appropriate or suitable for the specific project under consideration. In the following chapter, sub-phase B of the design synthesis approach will be executed, which is aimed at validating the CVSIT by applying a case study and conducting semi-structured interviews.

Chapter 7: Validation process

In this chapter, sub-phase B of the design synthesis phase of the systems engineering approach is conducted, which entails validating the developed decision support tool, the CVSIT.

In this research inquiry, the research problem, i.e. the absence of an effective PV system within the environment of MPP drug provision systems, was addressed by developing a decision support tool that facilitates the process of developing and implementing a context-specific PV system that will assist with the effective and efficient reporting of ADRs within the context of the MPP drug provision systems, while taking into consideration the niche factors. Such a system is thus proposed by developing an index, the Vigilance System Component-Intervention Index, which provides a guideline for the implementation of a Vigilance System. This index creates an outline of the various components that should be addressed in such a Vigilance System. Building on this, an operation tool, the CVSIT, was developed during sub-phase A of the design synthesis that provides a drug provision project within the context of the MPP with a customised implementation strategy for a Vigilance System. However, in order to authenticate and evaluate whether the tool addresses the research aim, a validation process needs to be conducted.

In sub-phase B, therefore, a twofold validation approach was conducted that entailed (i) applying a case study and (ii) conducting semi-structured interviews with SMEs. In this chapter background information pertaining to the identified case study as well as the findings from the case study are presented, along with the processes, results, and recommendations from the semi-structured interviews. Refer to Figure 7.1 for an overview of this process and how it relates to the rest of the research inquiry.

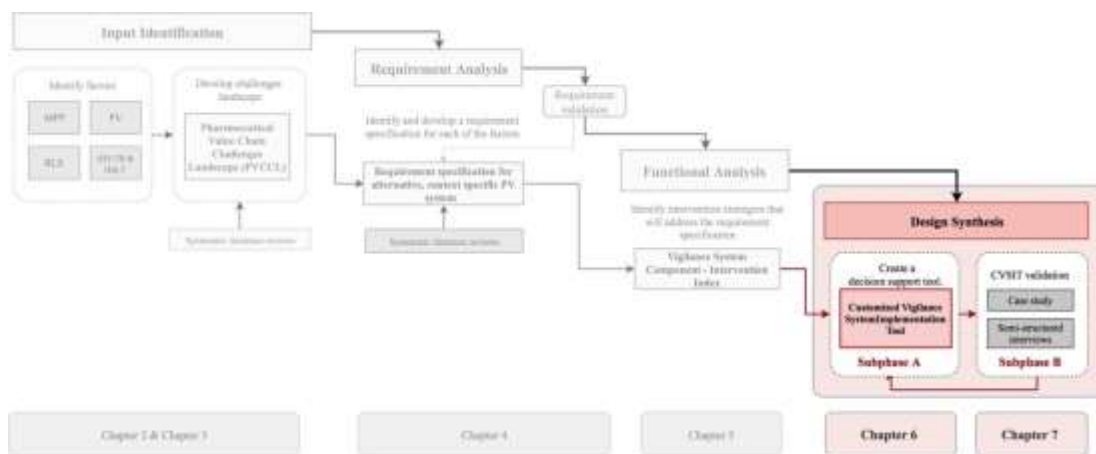


Figure 7.1: Systems engineering approach: Design synthesis, subphase B

7.1 VALIDATION APPROACH OVERVIEW

According to the IEEE-STD-610 guidelines, a validation process is the process of evaluating the developed system, model or component to ensure that the expectations, stated at the

beginning of the process, are met (IEEE Standards Board, 1990). Thus the final phase of the design synthesis phase in the systems engineering approach, is to validate the CVSIT, which was developed to assist drug provision projects (for example pilot, roll-out, and/or existing drug provision projects) to formulate customised implementation strategies for a Vigilance System (refer to Chapter 6), with the aim of improving drug safety reporting and monitoring. The focus of the validation is to determine if the CVSIT would be an effective tool to assist with the effective and efficient reporting of ADRs within the environment of MPP drug provision systems.

In this section, an overview is presented of the purpose of the validation approach, within the context of this research, followed by a discussion of the applied validation methods.

7.1.1 Validation purposes

As mentioned, the aim of the validation process within this research context is to determine if the CVSIT meets the required expectation, i.e. the research aim – assisting with the efficient and effective reporting of ADRs by proposing a context-specific PV system for MPP drug provision systems. In order to determine this, there were three purposes for the validation of the CVSIT, namely:

- i. Evaluating the *applicability* of the CVSIT, where applicability refers to the quality of the tool being relevant to the context of the MPP drug provision systems considering real world situations;
- ii. Evaluating the *practicality* of the CVSIT, defined as the quality of being suitable for a specific objective. Within this dissertation, the practicality of the CVSIT was aimed at evaluating the tool in terms of its ease of use and to what extent it was intuitive to understand; and
- iii. Evaluating the *value* of the CVSIT within the context of drug safety monitoring and PV systems. Thus, within the context of this dissertation it is to determine if the CVSIT is a value-added tool that enhances the current traditional PV system.

7.1.2 Validation methods approach

In order to address the validation purposes, as discussed in Section 7.1.1, the validation process included two approaches: (i) applying the CVSIT to a case study, and (ii) conducting semi-structured interviews with SMEs in the fields of pharmaceuticals and PV.

A retrospective case study was applied with the aim of determining whether the outcomes from the CVSIT corresponded to a previously documented case, in order to ascertain whether the CVSIT might be an effective tool to use for ADR reporting within the context of MPP drug provision systems. Thus, a customised implementation strategy for a Vigilance System, developed using the CVSIT, was compared with the actual PV plan executed for the case, and the respective outcomes are subsequently compared.

The second validation process entailed validating the CVSIT by conducting semi-structured interviews with SMEs using the case study to illustrate the operability of the tool. SMEs were contacted to discuss and assess the applicability, practicality and the value of the CVSIT with respective reporting of ADRs within the context of the MPP drug provision systems.

In this chapter, the approaches, results and inferences drawn from the respective validation processes are discussed.

7.2 VALIDATION PROCESS 1: THE CASE OF BEDAQUILINE

For this research inquiry a retrospective case study was applied. This is a type of case study in which the data is collected after the specific event or activities have occurred, and the final outcomes and events are known (Street and Ward, 2012). The main reasoning for conducting a retrospective case study is to evaluate whether the CVSIT can effectively develop an implementation strategy for a Vigilance System that has been implemented in a real world scenario, deducing that the tool would be effective in addressing the implementation of a context-specific PV systems that will assist with the effective reporting of ADRs. Furthermore, the case study also sought to determine whether the CVSIT would be able to address shortfalls or improve the strategy that was developed and implemented during the relevant case.

The selection of the case is one of the most essential parts of case study research, as the selected case should be relevant and provide sufficient information with regard to the research objective being investigated (Bleijenbergh, 2012). For the purpose of this research, therefore, the objective of the case study was to evaluate whether the CVSIT would be useable tool for ADR reporting, i.e., whether the CVSIT would be able to effectively facilitate the process to develop an implementation strategy for a Vigilance System that could be implemented in real world situations. Furthermore, as this research inquiry considers the context of the MPP drug provision system, evaluating the applicability would also look at to what extent the CVSIT considers and accommodates the context-specific factors. Thus, to identify an appropriate case study, the following selection criteria were developed:

- i. The case had to be retrospective in nature;
- ii. Information related to the drug safety monitoring or PV system implemented for the drug provision project had to be available;
- iii. Information on the specific drug provision project (related to the patients and resource availability) had to be available; and
- iv. The case should be deemed representative of the context of the MPP drug provision system; thus the case should be (i) within an environment where the MPP is active, (ii) in the context of RLS, and (iii) considering the disease burden addressed by the MPP (i.e. HIV, TB or Hepatitis C).

Using these criteria as a guideline to identify a case study, it was evident that the roll-out of Bedaquiline, a drug used in the treatment of multi-drug resistant TB (MDR-TB) in the context of South Africa meets all the identified requirements. The roll-out of Bedaquiline in South Africa occurred in 2012, which means that the case could be applied as a retrospective case study. Furthermore, the case for the roll-out of Bedaquiline has been thoroughly documented in the literature, and information was readily accessible about both the drug safety requirements, as stated by the WHO, and about the context-specific information related to the project, i.e. where the project was rolled out, what resources were available and what additional information on the specific drug existed (Conradie *et al.*, 2014; WHO, 2015b; Jones *et al.*, 2019). As the selected case study was conducted in South Africa and regarded as a roll-out of medication for TB, it also falls within the environment of MPP drug provision systems,

given the environment where the MPP was launched, i.e. South Africa (Medicines Patent Pool, 2010a); in addition, it considers a disease specifically addressed by the MPP, i.e. TB (Medicines Patent Pool, 2010a), and it relates to RLS, i.e. South Africa is a country with access to limited resources within the healthcare landscape (Mathlathi *et al.*, 2015).

Furthermore, a multiple organisation approach (Street and Ward, 2012) was used to conduct a comparable process to determine the applicability of the CVSIT. This approach is appropriate when investigating what the outcomes of different organisations are (in the case of this research, it was drug provision projects) when using the same tool (Street and Ward, 2012). Thus, for the purpose of this research, two case studies were applied, namely, Case A, which considers the cohort launch of Bedaquiline in South Africa, and Case B, which investigates the countrywide roll-out of Bedaquiline, also in South Africa. Both cases concerned the provision of the drug, Bedaquiline, but did so in different environments with regard to area, patients, and resource availability.

7.2.1 Background of case studies

TB treatments were often found to be prolonged and have poor outcomes and thus, in 2012, under the provision of accelerated approval by the Food and Drug Administration (FDA) Bedaquiline was introduced for multidrug resistant TB (MDR-TB) treatments. Bedaquiline was the first new drug to be released in the last 50 years for such TB treatment (Jones *et al.*, 2019). The WHO recommended the roll-out of Bedaquiline, but advised that PV systems needed to be robust to actively monitor Bedaquiline (Jones *et al.*, 2019). Bedaquiline was initially released under controlled access to 6 different countries, South Africa being one, in 2012. This controlled access program was known as the Clinical Access to Bedaquiline Programme (BCAP). However, after successful and favourable outcomes, in June of 2018, South Africa integrated Bedaquiline into the MDR TB treatment regime (MSF| Doctors Without Borders, 2018). Figure 7.2 depicts a timeline for the roll-out of Bedaquiline within the South African context.

For the purpose of this research, it was decided that the CVSIT would be applied to two cases for the roll-out of Bedaquiline. The first case, Case A, refers to the BCAP of 2012, while Case B refers to the countrywide roll-out of 2018. The reasoning behind this was to identify if and how the customised implementation strategy for a Vigilance System as developed using the CVSIT, would change when considering the same drug, Bedaquiline, but in different environmental conditions, i.e. different target patient groups, facilities, etc.

In this section, background is provided on the roll-out of Bedaquiline for both cases, followed by the actual PV plan developed and implemented for the respective cases, and the outcomes from the application of the CVSIT to the respective cases. A comparison is then made between the actual plan and the implementation strategy developed using the CVSIT for both cases.

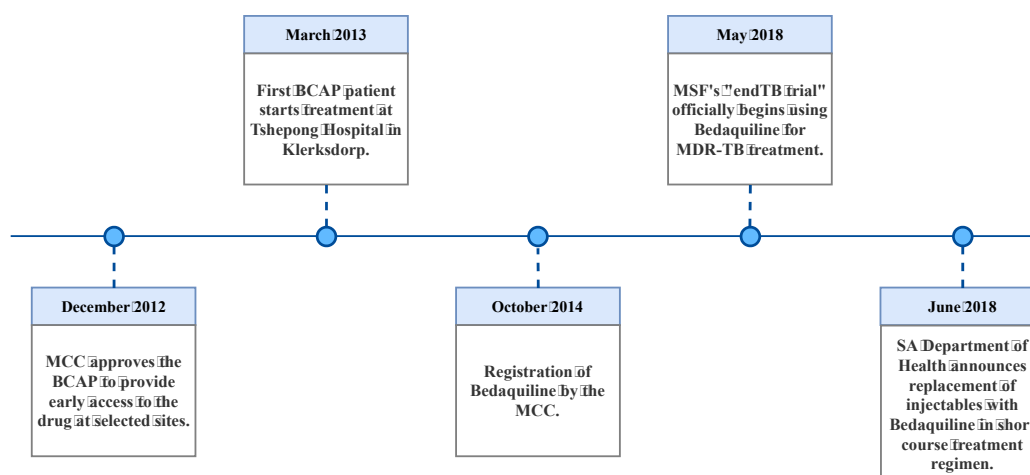


Figure 7.2: Timeline for Bedaquiline launch in South Africa

7.2.2 Case A: Clinical access to Bedaquiline programme

In South Africa in 2010, 14 161 case of of multi-drug resistant (MDR) TB were reported, of which 10% were cases of extreme drug resistant TB (XDR-TB). However, in 2012, after accelerated approval, a new drug, Bedaquiline, was authorised by the US Food and Drug Association (FDA) for the treatment of MDR-TB (Conradie *et al.*, 2014).

Although Bedaquiline was not yet approved by the South African Medical Control Council (MCC) at that stage, through an early access program, some patients with little or no other treatment options were granted access to Bedaquiline through the drug manufacturers Janssen Pharmaceutica (Conradie *et al.*, 2014; MSF| Doctors Without Borders, 2018). Thus, under a controlled early access program, referred to as BCAP, a few countries including South Africa made available Bedaquiline to selected patients with drug resistant TB, including MDR and XDR-TB (Conradie *et al.*, 2014). Selection criteria were used to determine which patients would be allowed to participate in the study. The selected patients had to be older than 18, be resistant to at least 3 anti-TB drugs and not be pregnant or breastfeeding (Clayden, 2014; Ndjeka *et al.*, 2015). In 2013, the program was launched in 5 sites across South Africa, with Tshepong hospital in Klerksdorp being the first site; due to favourable outcomes, this was later extended to 12 sites (Clayden, 2014; Health-e News, 2018; The Union, 2018). In 2014, the MCC approved the nation-wide roll-out of Bedaquiline within the National TB program (Clayden, 2014).

This document has been prepared to serve as a guideline to those reporting ADRs. It represents the MCC current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. The MCC reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge that is current at the time of consideration of the safety data.

In Section 7.2.2.1. the PV plan that was executed for the BCAP will be discussed, after which in Section 7.2.2.2. the implementation strategy for a Vigilance System, as developed using the CVSIT, will be discussed. Lastly a discussion regarding the findings with respect to Case A will be drawn together.

7.2.2.1 Actual PV plan executed for Case A

Since Bedaquiline was a novel drug being rolled out for the first time, it was of utmost importance that effective pharmacovigilance plans and drug safety monitoring systems were in place (WHO, 2013; Jones *et al.*, 2019). When Bedaquiline was launched as part of the TB treatment plan in the Western Cape, HCPs were encouraged to report all suspected ADRs to the Western Cape Pharmacovigilance Programme, a spontaneous reporting system for suspected ADRs related to TB and HIV treatments (Mehta, Dheda, Steel, M Blockman, *et al.*, 2014; Medicines Control Council of South Africa, 2017; Jones *et al.*, 2019). The BCAP collected reports on serious ADRs, deaths and/or birth defects. The BCAP is a collaboration between the Western Cape Province Department of Health and the University of Cape Town's Division of Clinical Pharmacology (Jones *et al.*, 2019).

For the BCAP, a structured reporting form was used to obtain the following information regarding the patient: age, sex, weight, pregnancy status, HIV status, co-morbidities, and medical history (Medicines Control Council of South Africa, 2017; Jones *et al.*, 2019). The reports also acquired information on the suspected ADRs, management of the ADR and relevant laboratory investigations. The data were then captured, and a pharmacist would perform the initial assessment and contact the patient if additional information was required. As mentioned, during the first year, HCPs treating drug resistant TB were actively encouraged and reminded to report any suspected ADR. The causality assessments of the suspected ADRs were monitored by the WHO Uppsala Monitoring Centre (Jones *et al.*, 2019).

In order to assist countries with the roll out of Bedaquiline, the WHO set up an implementation plan, that included guidelines on the implementation of a PV system (WHO, 2013, 2015a). These guidelines emphasise the importance of some form of reporting and PV systems, as Bedaquiline is a newly released drug and should thus be monitored particularly carefully. These guidelines provide a short overview of the three main methods of pharmacovigilance to be considered, namely spontaneous reporting³³, targeted spontaneous reporting³⁴ and cohort event monitoring³⁵ (WHO, 2015b). The guidelines state that, when deciding which method to implement, the existing PV systems in the relevant should be considered. However, it also states that, when introducing Bedaquiline, a more active approach is advised, such as CEM. Moreover, reporting forms should be made available and staff should be trained appropriately (WHO, 2013, 2015b).

In the context of this research study and the CVSIT, however, the WHO implementation plan did not consider certain factors, and thus there is a valid case to propose the implementation of a Vigilance System by applying the CVSIT. Furthermore, the WHO recommendations do not consider the possible different environment capabilities where the projects were launched, i.e. the resource availability and capabilities, the patients' knowledge and the availability of facilities, whereas the CVSIT can provide a customised implementation plan for the specific project in the specific setting.

³³ Spontaneous reporting is the most common form which entails having a healthcare practitioner or the patient reporting a suspected ADR. This is a passive form of reporting.

³⁴ Targeted spontaneous reporting is a more active form that monitors a specific set of safety concerns for a predefined population.

³⁵ CEM is a form of active monitoring which is used to monitor ADR in patients receiving a specific medication or treatment.

7.2.2.2 *An implementation strategy for Case A using CVSIT*

To complete the vigilance profile assessment (i.e. Dimension 1 of the CVSIT), information regarding the project, the patient and resource availability was required. From the background information on the BCAP, as defined in Section 7.2.1, the data for the project information and the patient information sections could be identified. Considering the Tshepong Hospital as one of the first sites, and assuming that the other sites were in similar settings and environments, conclusions could be drawn for the profile assessment data regarding the human and technological resources.

In Appendix G, Section G.1, the vigilance profile assessment data for Case A can be found along with the resources used, and the Excel based form for the vigilance profile assessment can be seen in Appendix G, Section G.2.

The vigilance implementation strategy for Case A provided multiple intervention strategies for each of the vigilance components, except for the component of novel technologies. This is because this case does not have the required technical or human resources to implement these interventions at the given stage of the project. Furthermore, additional information was included regarding certain intervention strategies related to the reporting process, communication and education (i.e. that the reporting form should specifically mention Bedaquiline, that the HCP should be educated about the context of the drug before considering certain reporting processes such as CEM or TSR). The comprehensive / complete customised implementation strategy for a Vigilance System for the Case A can be found in Appendix G.

7.2.2.3 *Discussion of Case A findings*

When considering the Vigilance System developed with the CVSIT for Case A, a comparison can be drawn between the actual PV plan developed and implemented for the BCAP and the implementation strategy for a Vigilance System developed by using the CVSIT within the context of the BCAP. The intervention strategies for both the actual PV plan that was executed and the CVSIT Vigilance System's implementation strategy is summarised in Table 7.1.

From these results, it is firstly identified that, for the actual PV plan, the following vigilant components, as discussed in Chapter 5, were addressed and intervention strategies for each of these components were implemented: (i) modes of reporting, (ii) reporting process, (iii) databases, (iv) responsibilities and accountability and (v) education. When comparing these five components with the outcomes found using the CVSIT, it was found that the CVSIT identified the same intervention strategies as the actual PV plan. This reaffirms that the CVSIT is correctly able to analyse the profile of the project and adequately identify intervention strategies best suited to the project in a real-life situation. Furthermore, although the CVSIT did identify the same intervention strategy for the components of the reporting process as actually implemented in the PV system for the BCAP, the CVSIT also identified additional interventions that could have been investigated. In the BCAP spontaneous reporting was implemented, although the WHO recommended that more active reporting should have been considered, such as CEM. The CVSIT implementation strategy indicated that CEM, TSR and black triangle reporting could all have been investigated further.

Moreover, when considering the PV plan that was executed, the following Vigilant System components were not directly addressed: (i) response strategies, (ii) awareness, (iii) communication, (iv) quality management, and (v) novel technologies. Additionally, although

the actual PV plan did consider the Vigilant System components of education, and responsibility and accountability, direct intervention strategies were not implemented, as HCP were only encouraged to report ADRs, but no clearly defined proposed strategies were provided. However, when reviewing the implementation strategy developed by using the CVSIT, these Vigilant System components were addressed, and multiple intervention strategies were identified for each component. The only vigilant component that delivered no intervention strategies was novel technologies, and this is due to the profile of the BCAP focusing on the reporting of ADRs and not focusing on the incorporation of expanding technologies.

Table 7.1: Case A: actual PV plan comparison with implementation strategy for Vigilance System

Case A: BCAP			
Vigilant component		Actual PV plan executed	CVSIT Vigilance System implementation strategy
Direct components	Mode of reporting	Paper-based, Web-based reporting forms	(i) Paper-based, (ii) Web-based reporting forms
	Reporting process	Spontaneous reporting but WHO recommended CEM	(i) Spontaneous reporting, (ii) CEM, (iii) TSR, (iv) Black triangle reporting, (v) 3-step approach (vi) Task-shifting
	Databases	Vigibase	(i) Vigibase, (ii) Physical storage
	Response strategy	Not addressed	(i) Feedback using ICT (ii) Policy & guidelines
Supporting components	Awareness	Not addressed	(i) Paper-based resources, (ii) Communities of practices
	Communication	Not addressed	(i) Communication network, (ii) Email, (iii) Videoconferences, (iv) Paper-based (v) Policy & guidelines
	Education	No direct interventions implemented the WHO only suggest that HCP should be educated	(i) Web-based, (ii) Patient information cards, (iii) Short courses, (iv) Paper-based
	Quality management	Not addressed	(i) Audits, (ii) Policy & guidelines, (iii) Monitoring sectors
	Responsibility & accountability	HCP urged to report ADRs	(i) PV stakeholder policy, (ii) All incentive schemes
Additional factors	Novel technology	Not addressed	No intervention strategies identified

7.2.3 Case B: Countrywide roll-out of Bedaquiline

In 2018 the Department of Health announced that Bedaquiline would be implemented for standard MDR TB treatment regimens across South Africa, thus replacing the injectables, which were often associated with harsh side effects (Global TB Community Advisory Board, 2018; SAnews, 2018). The Department of Health made the decision to implement the countrywide roll-out, which is wider than recommended by the WHO, in an attempt to improve the high TB burden in SA.

This case differs from Case A, as certain project and patient information changed when Bedaquiline was rolled out to the entire country. With Case A there was more control over the

patients taking the drug, but in Case B any TB patient could, in theory, access the drug. The project was also more focused on the entire culture of reporting. Thus, the CVSIT was used to determine a Vigilance System's implementation strategy for Case B and to explore how the CVSIT implementation strategy compares to that of the actual PV plan executed for Case B.

As with Case A, firstly in Section 7.2.3.1 the PV plan that was executed for the countrywide roll-out will be discussed, after which in Section 7.2.3.2 the implementation strategy for a Vigilance System using the CVSIT will be discussed, and final concluding remarks will be discussed.

7.2.3.1 Actual PV plan developed and implemented in Case B

For the countrywide roll-out, which took place in June of 2018, a very similar drug safety reporting and monitoring system was implemented as had been done with the cohort roll-out of Bedaquiline (Case A). As South Africa made use of spontaneous reporting for most of the PV systems, this mode of reporting was implemented for this case too (Jaramillo, 2015; Medicines Control Council of South Africa, 2017). The WHO, however, still recommended active modes of reporting to be implemented (Jaramillo, 2015; Stop TB Partnership and Medecins Sans Frontieres (MSF), 2015; MSF| Doctors Without Borders, 2018). Furthermore, as with Case A, web-based reporting forms were implemented to report ADRs and Vigibase was used to capture and monitor these reported ADRs (Jaramillo, 2015; Stop TB Partnership and Medecins Sans Frontieres (MSF), 2015; WHO, 2015b). With regard to this specific project, no customised intervention strategies were implemented for a Vigilance System, as specified in Chapter 5, with regard to the supporting components, i.e. education, response strategies, awareness, and quality management, or the additional factors, i.e. novel technologies.

7.2.3.2 Implementation plan using CVSIT in Case B

In Case B, the CVSIT tool was applied to a countrywide roll-out of Bedaquiline to treat MDR TB. As with Case A, information on the project was gathered from the literature to complete the Vigilant Assessment section of the CVSIT. This information can be found in Appendix H, Section H.1. Although for Case B the same drug, Bedaquiline, was used as in Case A, certain project profile changes required the implementation plan to be adapted. These profile changes were that for Case B Bedaquiline was being rolled out over the whole country, and thus there was not as much control over the patients taking the drug as there had been with Case A.

Considering the customised implementation strategy for a Vigilance System for Case B, multiple intervention strategies were once again identified for the different vigilance components. CVSIT Excel document for Case B can be found in Appendix H, Section H.2.

7.2.3.3 Discussion of Case B findings

When considering Case B, the countrywide roll-out of Bedaquiline, similar inferences were made as with Case A. The PV plan for the countrywide roll-out that was actually implemented as well as the strategy developed using the CVSIT can be found in Table 7.2. For the actual PV plan, once again three of the direct components were addressed, namely modes of reporting, reporting process, and databases. As with Case A, the CVSIT identified the same intervention strategies for these components as had been executed in the PV plan for the countrywide roll-out of Bedaquiline, thus validating that the CVSIT is able to effectively identify intervention strategies that were implemented in the real-world situations.

Furthermore, as with Case A there were certain vigilant components that were not addressed at all in the actual PV plan, but the CVSIT was able to identify multiple intervention strategies for these components.

Table 7.2: Case B actual PV plan comparison with implementation strategy for Vigilance System

Case B: Countrywide roll-out			
Vigilant component		Actual PV plan	CVSIT Vigilance System implementation strategy
Direct components	Mode of reporting	Paper based Web based	(i) Paper based, (ii) Web based
	Reporting process	Spontaneous reporting but WHO recommended CEM	(i) Spontaneous reporting, (ii) 3-step approach, (iii) Task shifting
	Databases	Vigibase	(i) Vigibase, (ii) Physical storage
	Response strategy	Not addressed	(i) Feedback using ICT, (ii) Policy & guidelines
Supporting components	Awareness	Not addressed	(i) Paper-based resources, (ii) Communities of practices, (iii) Collaboration & partnerships
	Communication	Not addressed	(i) Communication network, (ii) Email, (iii) Videoconferences, (iv) Paper based, (v) Policy & guidelines
	Education	Not addressed	(i) Web-based, (ii) PV curriculum, (iii) Patient information cards, (iv) Short courses, (v) Paper-based
	Quality management	Not addressed	(i) CVP, (ii) Audits, (iii) Policy & guidelines, (iv) Addressing GMP & GDP, (v) Monitoring sectors
	Responsibility & accountability	Not addressed	(i) PV stakeholder policy, (ii) Incentive schemes: Financial, career performance, positive working environment, benefits & support
Additional factors	Novel technology	Not addressed	No intervention strategies identified

7.2.4 Discussion of case studies A and B

Although both cases considered the same drug, there were profile changes with regard to the respective contexts, such as the control over the patients and the areas where the drug were being rolled out. Thus, when comparing the CVSIT implementation strategy for Case A and Case B, further inferences may be made regarding the customisation of the intervention plans in different scenarios. When comparing the two cases (refer to Table 7.3), differences with regard to the intervention strategies can be identified; the vigilant components relating to (i) the reporting process, (ii) awareness, (iii) education, (iv) quality management, and (v) responsibility & accountability differ between Case A and Case B, because Case A was conducted in a cohort format, whereas Case B was focused on a countrywide roll-out. Furthermore, for the components of awareness, education, and quality management, Case B additional intervention strategies were proposed using the CVSIT. The main reason for this is that Case B focuses more on creating a culture of reporting of ADRs.

Based on this comparison, additional attributes of the CVSIT may thus be inferred. Firstly, it is evident that the CVSIT does not only develop an implementation strategy for a project, but

creates a *customised* implementation strategy best suited to the specific project. Secondly, it reaffirms that the CVSIT is robust enough to adapt to the specific environment with regard to the patients and the specific drug being considered. Thus, the comparison also reaffirms the need to readdress a PV system or Vigilance System when there are profile specific changes.

Table 7.3: Comparison between CVSIT implementation strategies for Case A and Case B

Comparison between CVSIT implementation strategies for Case A and Case B			
Vigilant component		Differences	Intervention strategies that changed
Direct components	Mode of reporting	Same interventions	
	Reporting process	Changes in interventions	The following were only advised for Case A: (i) CEM, (ii) TSR, (iii) Black triangle reporting
	Databases	Same interventions	-
	Response strategy	Same interventions	-
Supporting components	Awareness	Changes in interventions	The following were only advised for Case B: Collaboration & partnerships
	Communication	Same interventions	-
	Education	Changes in interventions	The following were only advised for Case B: PV curriculum
	Quality management	Changes in interventions	The following were only advised for Case B: (i) GVP, (ii) Addressing GMP & GDP
	Responsibility & accountability	Changes in interventions	The following were only advised for Case A: (i) Workload management, (ii) Flexible working arrangements
Additional factors	Novel technology	Same interventions	-

7.2.5 Summary of case study

By conducting these two different case studies on the roll-out of Bedaquiline in South Africa, the following attributes of the CVSIT could be validated:

- i. The CVSIT is able to effectively identify intervention strategies for a Vigilance System that has been implemented in real world situations;
- ii. The CVSIT was able to identify additional components that were not implemented or considered in real world situations;
- iii. The CVSIT is able to develop a *customised* implementation strategy for a specific project and
- iv. The CVSIT is robust enough to adapt to changes in a project's context.

To further evaluate the CVSIT, semi-structured interviews with SMEs were conducted. This process and the results from the validation are discussed in the following section.

7.3 VALIDATION PROCESS II: SEMI-STRUCTURED INTERVIEWS WITH SUBJECT MATTER EXPERTS

In this section, the semi-structured interview process of the CVSIT validation is discussed. In these semi-structured interviews, six SMEs from various backgrounds relevant and/or related to PV, MPP and or pharmaceuticals, took part in validating the CVSIT. The aim was to evaluate the applicability and practicality of the tool to assist with effective and efficient reporting of ADRs within the environment of MPP drug provision systems, as well as to determine if the tool adds value to PV and drug safety monitoring.

In this section, the semi-structured interview process, validation results and findings as well as possible refinements are discussed.

7.3.1 Semi-structured interview process

The semi-structured interviews were conducted in two steps: firstly, the SMEs were given pre-read documents, and secondly, they replied to the validation questions in Skype interviews (the pre-read document and validation questionnaire can be seen in Appendices I, Section I.1 and I.2 respectively). SMEs were contacted via email to determine their willingness to assist with validating the CVSIT and, on reply, they were sent the pre-read documents to work through. For an overview of the qualifications and background experiences of the different SMEs who assisted with the validation, refer to Table 7.4.

Two sets of pre-read documents were provided to them: the first set of documents introduced the background of the research, a short overview of the different dimensions of the CVSIT, and instructions on the operation of the CVSIT. Accompanying this document was the Excel CVSIT document, which the SME could access and operate. The second set of documents provided information on the two case studies of the roll-out of Bedaquiline that had been conducted, as documented in Section 7.2, to illustrate the operations of the tool. These documents, with reference to the case studies, contained information on Bedaquiline and the actual PV plans executed during the roll-out of the drug for both the BCAP (Case A) and the countrywide roll-out (Case B). Furthermore, these documents also included the customised implementation strategy for a Vigilance System developed by using the CVSIT along with the Excel CVSIT documents for each of the respective cases, Case A and Case B.

The SMEs were then contacted via Skype for a validating question-based interview to verify the operability and practicality of the CVSIT. During these interviews, a short presentation was given, summarising the content of the pre-read documents, to ensure that the SMEs understood the aim, dimensions and functions of the CVSIT. A demonstration on the operability of the CVSIT was then given, via Skype, using a presentation and the case study, as documented in Section 7.2, after which the case studies and findings were presented. The validation questionnaire, shown in Appendix E, was then completed. The questionnaire was aimed at evaluating the practicality of the CVSIT and the applicability of the tool in real world situations. A 5-point Likert scale was used to rate the responses to the questions. In the following section, the results from the validation process are presented, with an overview of the different recommendations that were made.

Table 7.4: SME qualification and background information

SME number	Degree/Qualification	Background experience
1	MB, BS in Medicine	Board member and treasurer of ISoP (from 2016 to the present) Principal consultant at the NDA Group AB, a drug development consultancy company (from 2007 to the present) The deputy qualified person of PV at Johnson & Johnson (2005 – 2007) The Senior Medical Assessor of the Medical and Healthcare products Regulatory Agency of the United Kingdom (1994 – 1999)
2	BSc (Hons) MPH Epidemiology PhD Clinical Pharmacology	Head of clinical research at University of Cape (from 2002 to the present) Clinical operations manager at i3 Research, a global pharmaceutical services company (1998 – 2002) Clinical research Associate at Novo Nordisk, a global healthcare company focused on treatments related to chronic diabetes (1996 – 1998) Coordinator of Global Pharmacovigilance open-access collaboration
3	BSc in Biochemistry	Deputy Qualified Person for Pharmacovigilance at Salom Pharmacy Ltd Ghana (from 2017 to the present) Lab officer at Wenchi health centre, a healthcare facility in Ghana (2014 – 2015)
4	Bachelor's degree in Applied Biology Master of Science in Clinical Trials program PhD Candidate	PhD research in Pharmacovigilance at the University of Sheffield, School of Health and Related Research (from 2014 to the present) Member of ISoP Member of the Clinical Human Factor Group, a charity aimed at improving the healthcare environment Member of the Pharmaceutical Information and Pharmacovigilance Association Member of Pharmaceutical and Human Factor Group an organisation focused on the systems within a pharmaceutical industry
5	Bpharm MSc in Pharmaceutical Affairs MBA	Senior Manager at Guidehouse, a management consulting firm servicing the public and commercial sectors, within the department of Medicine Selection and Use (from March 2019 to the present) Senior Technical Advisor at Management Sciences for Health a global non-profit organisation focused on developing sustainable health systems (2017 – 2019) Pharmacy technical assistance manager for Right to Care, a non-profit organisation aimed at pioneering solutions related to treatments for HIV and associated diseases (2015)
6	MBChB BSc(Hons) FCCP(SA) Mmed(Clin Pharm) PhD	Medical Specialist: Clinical Pharmacologist at Stellenbosch University (from 2013 to the present) Professor and coordinator of undergraduate clinical pharmacology at the Faculty of Medicine and Health Sciences of Stellenbosch University

7.3.2 Semi-structured interview validation results

The results from the semi-structured interview process with the SME are provided in this section. Each of the questions, from the questionnaire found in Appendix I, are summarised and the main findings are discussed in more detail.

The questionnaire contained eight questions, which evaluated the applicability and the practicality of the tool within the context of developing a context-specific PV system for use in MPP drug provision systems. Furthermore, the questionnaire was aimed at identifying possible weakness and/or strengths of the tool. The first five questions made use of a 5-point Likert scale, to gain a holistic overview of the tool, the terminology and intuitiveness to

understand the concepts of the tool, and the targeted audience group. The subsequent two questions sought to identify any strengths or weaknesses of the tool, and the final question considered the value of the CVSIT with respect to drug safety monitoring in a real-world case.

The results of the first five questions are summarised in Figure 7.3. From the results of Question 1, it can be seen that the SMEs were in agreement that the CVSIT provides a holistic approach for the implementation of a Vigilance System for a context-specific PV system, specifically for drug provision projects within the context of the MPP drug provision systems. Furthermore, it was found that, although the CVSIT is applicable to the environment of MPP drug provision systems, it could also be applied to other similar environments and other related diseases, if adaptations are made to it.

With reference to Question 2, the SMEs also agreed that the CVSIT can provide a holistic overview not only of the direct components for ADR reporting but of accompanying and supporting components that are often disregarded in traditional PV systems. It was found that the CVSIT provides a novel approach to addressing PV systems that challenge the conventional drug safety monitoring systems.

When considering the CVSIT in terms of ease of use and intuitiveness of understanding (Question 3), the SMEs were also in agreement. This confirmed the practicability of the tool in real world cases within the context of MPP drug provision systems.

With regard to Question 4, the level of experience required to operate the tool, there was some disagreement. 40% of the SMEs had a neutral perspective of the fact that very limited knowledge with respect to PV and drug safety monitoring was required. However, subsequent discussions revealed that the SMEs agreed that a rudimentary knowledge of PV or the system components of drug safety monitoring would be required to ensure the most effective operation of the tool. It was also found that, because the vigilance components are context-specific to PV systems, the user of the tool would need to understand the different components and processes related to PV.

Question 5, the last one, focused on the types of drug projects, within the context of the MPP drug provision systems, that the CVSIT would be targeted at, i.e. drug roll-outs, pilot drug projects, existing or established etc. The SMEs were in agreement that the CVSIT could be applicable to different projects within the context of the MPP drug provision systems, which reaffirmed that the CVSIT serves as a very good blueprint for the development of a universal tool that provides a holistic approach for a context-specific PV implementation strategy.

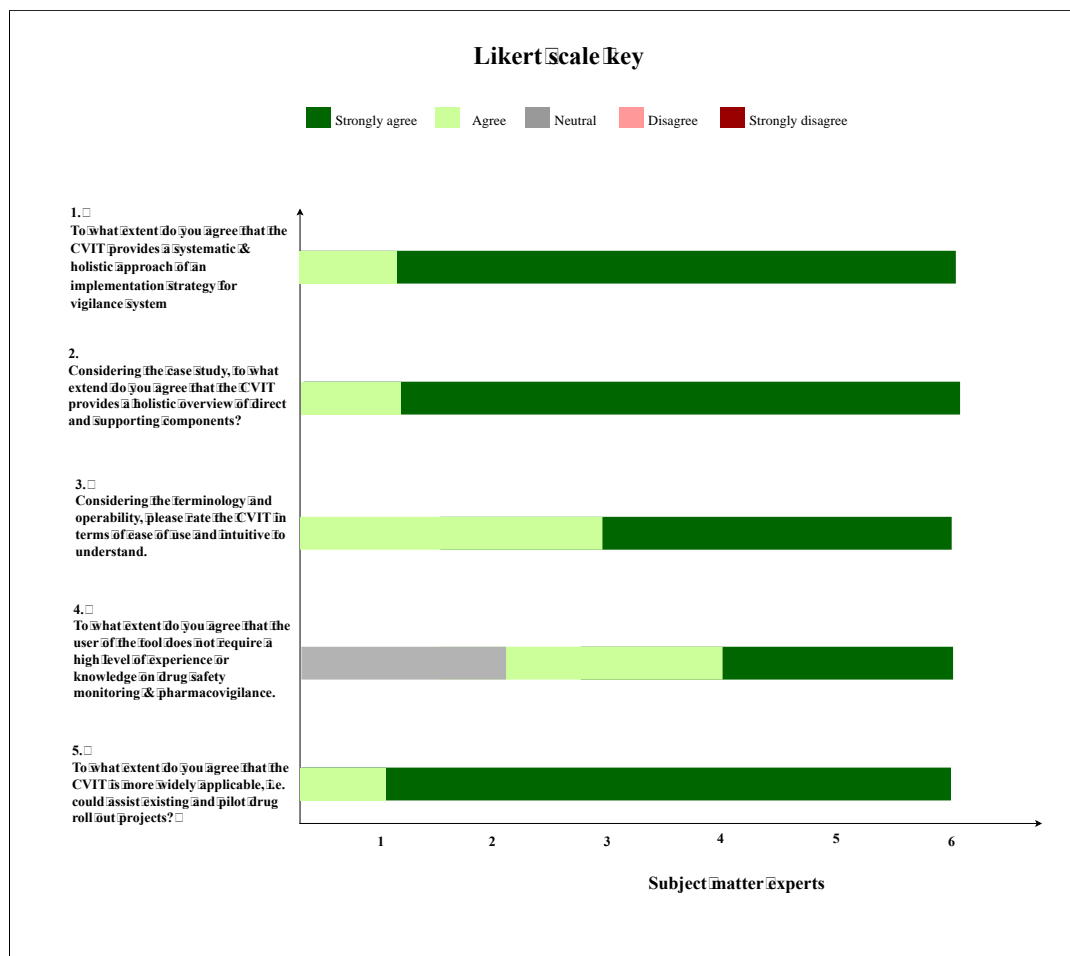


Figure 7.3: SME validation results for Questions 1 – 5

As previously mentioned, Questions 6 and 7 focused on identifying the strengths and weaknesses of the CVSIT, and the results are summarised in Table 7.5. The strengths identified confirmed that the CVSIT is a tool that can encompass all the components called for in a drug safety monitoring system. Furthermore, it is found that the tool is robust and agile, as it considers the patient aspect and is applicable to different environments, i.e. countries, drugs and population groups. Another strength that was highlighted, was that the tool provides a novel, systematic thinking approach for the development of a context-specific PV system. Furthermore, it was also confirmed that, although the CVSIT is targeted at audiences that implement PV systems for specific drug projects, i.e. regulatory authorities or national PV systems, it is not limited in its use to those specific audience groups and would be applicable to various stakeholders for different reasons. For example, it could be used by pharmaceutical companies to identify gaps or challenges related to their industry within the context of drug safety monitoring.

However, from the weaknesses identified, it can be deduced that, due to the broad applicability of the tool, there are country specific requirements that are lacking and that would have to be addressed when setting up a Vigilance System, such as incorporating a national PV regulation. Furthermore, it was also found that, as the CVSIT is developed for the specific context of the MPP drug provision systems, its use could be limited. However, it was also found that it could serve as a blueprint for a universal tool.

Table 7.5: Strengths and weaknesses of CVSIT identified through SME validation

What do you view as some of the key strengths of the CVSIT?	What do you view as some of the key weaknesses of the CVSIT?
<ul style="list-style-type: none"> i) Incorporating the patient aspect into the tool. The patient aspect is a key component in any PV system and incorporating it makes the system more robust. ii) The tool is also able to address specific patient and drug issues. iii) The tool is very easy to use and does not require a high level of experience or knowledge on pharmacovigilance or drug safety monitoring iv) The tool encompasses and captures all the components required for a PV system. This tool should be the first step to look at PV implementation strategies. v) The tool is broad enough to be applicable to different countries and stakeholders. For example, pharmaceutical companies, National Health Departments or medicine regulatory bodies can make use of the tool for various different reasons. vi) It's a comprehensive tool that is also context-specific to different environments. vii) The tool leads you through a systematic process of addressing and thinking about the different components and processes of a PV system. viii) It challenges the conventional PV systems and provides a novel thinking process of addressing a PV system. 	<ul style="list-style-type: none"> i) As the tool is very broad (not only specific to one country) there is the downfall of not implementing a specific country's national PV regulations. ii) Context-specific to niche factors.

The final question addressed the unique contribution of the CVSIT in the field of PV and focused on the identification of additional tools that could be used to complement the CVSIT. The SMEs agreed that they were not aware of any form of system modelling that has been conducted to the same detailed extent as in this study. To their knowledge, there was no such a tool with which the CVSIT could be compared. However, there were tools and frameworks identified that could be used to complement the CVSIT and to further strengthen the implementation state of a Vigilance System. These tools, similar to the CVSIT, provide guidelines and recommendations for the set-up of a PV system and can thus be used in alignment with the CVSIT to set up a Vigilance System for a specific drug project. The following tools were identified as possible complementary tools: (i) Indicator-Based Pharmacovigilance Assessment Tool (IPAT), (ii) the WHO PV Toolkit, and (iii) BioPhorum members-only organisation. A short description on each of these tools is provided.

Indicator-Based Pharmacovigilance Assessment Tool (IPAT)

The IPAT is a performance metric for PV systems that acts as a benchmark to identify gaps, diagnose strengths and weaknesses, and evaluate the different systems. The IPAT addresses 5 components, namely: policy, system structures, signal generation and data management, risk assessment, and risk management and communication, by assessing 43 indicators. The IPAT is intended to be used by government, medicine regulatory and public health programs to

diagnose and assess the performance of a PV and medicine safety system (Strengthening Pharmaceutical Systems (SPS) Program., 2009). The IPAT is thus a useful tool to use in conjunction with the CVSIT to assess an existing projects' PV system and identify possible shortcomings, after which the CVSIT can be used to identify possible intervention strategies to address these shortcomings.

WHO PV Toolkit

The toolkit gives an overview of the different practices within PV with the aim of providing PV practitioners in developing countries with access to trusted resources on PV related activities. The resources provided include the minimum set of requirements for a functioning PV system, and basic instructions on how to set up a PV centre, and manage the data (WHO, 2018a). However, the toolkit only provides an overview of these PV practices, and thus can be used mainly as an introductory tool to the implementation of a PV system, after which the CVSIT can be used to provide a more structured strategy for the implementation of such a system with customised intervention strategies.

BioPhorum

BioPhorum is an international members-only organisation that was established in 2014 with the aim of creating a communication forum for the global biopharmaceutical industry that fosters collaboration to accelerate progress within this industry (BioPhorum, 2014). To date, more than 82 member companies are part of this organisation, which connects industry leaders and delivers solutions by pooling knowledge, experiences and practices. BioPhorum has delivered solutions related to demand forecasting, quality improvement, and user implementation requirements for pharmaceutical manufacturing companies (BioPhorum, 2014). It is envisaged that collaboration with BioPhorum could improve the roll-out of the CVSIT within the pharmaceutical industry. Furthermore, in collaborating with this organisation, alterations could be incorporated into the CVSIT, as BioPhorum has a vast experience and knowledge base for the roll-out of tools and frameworks within the healthcare landscape.

In the following section, the refinements made by the SMEs during the validation process, as well as how such refinements were addressed, are discussed.

7.3.3 Refinements to the Customised Vigilance System Implementation Tool

During the validation process, the SMEs made certain recommendations regarding the applicability of the CVSIT, which were taken into account. These recommendations were reviewed and addressed either by reining the tool or considering these recommendations as possible future work, when such recommendations fall outside of the scope of this research study.

Suggested refinement 1: The inclusion of a pregnancy exposure registry as an intervention strategy

During the validation process, it was brought to the researcher's attention that a possible intervention strategy to include under the vigilant component of the reporting process, would be a pregnancy exposure registry. Pregnancy exposure registries are a cohort format study, where pregnant women who receive prescription biopharmaceutical products voluntarily allow the collection of information on the unborn child in order to compare the information

with women who do not take the same medication. This method allows for the improvement of safety information of medications, as the risk involved with the drug can be monitored. Furthermore, this study also allows not only for the assessment of the risk involved with the drug but also of the effectiveness of the drug (Gliklich RE, Dreyer NA and Leavy MB, 2014). As the CVSIT does consider the specific patient group, pregnant women, the inclusion of this intervention strategy is seen to be of value to the tool and thus incorporated into the CVSIT.

Suggested refinement 2: The component of education should be adapted to education & competency

During the validation process, it was mentioned that the vigilance component of education also addresses competency in the field of PV and that this aspect should be highlighted and incorporated. Competency refers to the possession of a sufficient amount of knowledge on regarding a topic, which for this dissertation is aimed at PV related knowledge. Thus, it was decided to adapt the wording of the vigilant component to education & competency.

Suggested refinement 3: Excluding text-based reporting as an intervention strategy

During the validation process, the recommendation was made by an SME to exclude text-based reporting as a possible intervention strategy as a mode of reporting due to the expert's experience and knowledge in that particular field. Text-based reporting has been found to be challenging in certain areas due to the language barrier. However, during this dissertation, it was found that this form of reporting is favourable in RLS, as stated in Section 5.11. The research found related to this intervention strategy reaffirms the effectiveness thereof in developing countries, and thus this recommendation was not incorporated into the CVSIT.

Suggested refinement 4: The inclusion of national PV guidelines

With regard to the applicability of the CVSIT in real-world situations, a recommendation was made that the tool needs to be restructured by incorporating the national PV guidelines for a specific country as stated by the regulatory authorities. However, as the CVSIT was developed for the broader purpose of being adaptable to various environments related to MPP drug provision systems, i.e. any RLS environment, the inclusion of a specific country's PV requirements would limit the operation of the tool. During the development of the tool the minimum set of PV requirements as stated by the WHO was taken into account. As this a valid recommendation to take into consideration when implementing the tool in a real-world situation, this recommendation should be considered as future work and will be discussed in the following chapter.

7.4 CONCLUDING REMARKS CONCERNING THE CUSTOMISED VIGILANCE SYSTEM IMPLEMENTATION TOOL

From the validation process with the SMEs regarding the applicability, practicability, and the value of the CVSIT, it was reaffirmed that the CVSIT is indeed an effective tool for developing an implementation strategy for a Vigilance System that considers direct, indirect and supporting components. Furthermore, due to the broad and robust nature of the tool, it could be implemented in various environments (i.e. countries, patients, drugs). However, this also limits the context specificity of the tool, as the CVSIT does not consider the different national regulations and guidelines of PV systems. Thus, these national regulations would have to be

used complimentary with the CVSIT to ensure that the implementation strategy developed by the tool considers the specific countries PV related.

Furthermore, the CVSIT is aimed at developing a customised implementation strategy for a Vigilance System based on the profile of the relevant drug provision projects; moreover, the audience group could comprise various stakeholders, from pharmaceutical companies and National Health Departments to medicine regulatory bodies that are, for various reasons, considering the implementation of Vigilance System.

It was also confirmed that the CVSIT does not require a high level of PV experience or knowledge; however, to ensure optimum use of the tool, the user would need a rudimentary understanding of PV or multiple users would need to be consulted.

From the semi-structured interviews, it was established that the CVSIT should be used as one of the initial tools when considering the implementation strategy of a PV system within the context of MPP drug provision systems, as it addresses the different components that such a system requires, in order to develop a *customised* implementation strategy within the context of the projects' unique requirements. However, as the tool is seen as an initial tool, complementary tools were identified that should ideally be used together with the CVSIT to ensure a more effective uptake of such a Vigilance System. These tools were identified as: (i) a country's specific national PV guidelines, (ii) the WHO PV Toolkit, and (iii) the IPAT.

7.5 CHAPTER 7 CONCLUSION

In this chapter, the developed tool, the CVSIT, was validated with the purpose of determining the applicability, practicability, and the value of the tool to assist drug provision projects with developing a customised implementation strategy for a Vigilance System. A two-step process was conducted that consisted, firstly, of a retrospective case study to illustrate the operation of the tool and determine the applicability and value of the CVSIT with respect to real-world situations, and secondly, semi-structured interviews were conducted with SMEs in the field of pharmaceuticals and PV. These validation processes reaffirmed the contributions of the CVSIT to the field of drug safety monitoring and PV.

Chapter 8: Conclusion and future work

In this chapter, closing remarks are made in respect of the research and its contributions to the pharmacovigilance industry, as well as its limitations and scope for possible future work related to the research.

8.1 OVERVIEW OF THE RESEARCH

In this research study, a decision support tool, the Customised Vigilance System Implementation Tool (CVSIT), was developed that facilitates the development of context-specific PV systems, a Vigilance System, within the context the MPP to subsequently contribute towards effective and efficient reporting and monitoring of ADRs.

In order to develop the CVSIT in a meticulous manner, the systems engineering approach was used. This is a comprehensive, iterative problem solving technique that begins by identifying an environmental need and analytically transforming it into a system solution (United States Government, 2001). In this thesis, it comprised four phases: (i) input identification, (ii) requirement analysis, (iii) functional analysis, and (iv) design synthesis.

In **Chapter 1**, the research study was introduced by discussing the background, the research rationale, the research aim and objectives, the scope, the research methodology, and finally the verification and validation process.

The first phase of the systems engineering approach, the input identification phase, entailed identifying and contextualising the different factors that had to be considered in developing a context-specific PV system. It was decided that an in-depth input investigation was not necessary, as the particular environment, in which the PV system would have to function (i.e. the MPP drug provision system), included four niche factors: (i) traditional PV systems, (ii) the MPP, (iii) HIV, TB and Hepatitis C, and (iv) RLS.

In **Chapter 2**, the first niche factor, traditional PV systems, was contextualised, and a systematic literature review identified the challenges associated with this factor and synthesised these into a challenges landscape within the context of PV systems. A similar approach was followed in **Chapter 3**, which focused on contextualising the other three niche factors, (i) the MPP, (ii) HIV, TB and Hepatitis C, and (iii) RLS. Challenges associated with these factors were identified and synthesised into a challenges landscape. The two landscapes of Chapter 2 and Chapter 3 were then integrated to develop an overarching challenges landscape in the context of MPP drug provision systems, referred to as the pharmaceutical value chain challenges landscape (PVCCL).

In **Chapter 4**, the second phase of the systems engineering approach was executed, namely the requirement analysis, in order to develop a requirements specification that would guide the development of the decision support tool. A preliminary requirements specification was developed from systematic literature reviews pertaining to each of the niche factors and by consulting the PVCCL to identify possible additional requirements to consider when addressing the challenges brought on by the niche factors. Thereafter, a verification process

was followed to authenticate the preliminary requirement specification. This entailed interviews with SMEs, who completed questionnaires related to the requirement specifications, within the context of each specific niche factor. The results were captured and analysed, and the necessary changes were made to develop a final requirement specification.

During the functional analysis, the third phase of the systems engineering approach, which is documented in **Chapter 5**, intervention strategies were identified by means of triangulation. Building on the findings from the intervention strategies, a Vigilance System was proposed as a context-specific PV system within the context of MPP. In order to guide the development of the decision support tool that facilitates the development of a Vigilance System, an index guide was synthesised, providing an overview of the various component and intervention strategies to consider when implementing a Vigilance System. This index guide is referred to as the Vigilance System Component – Intervention Index.

The final phase of the systems engineering approach, the design synthesis phase, was subdivided into two sub-phases (A and B). The aim was to develop a decision support tool building on the foundational features of the Vigilance System Component – Intervention Index. In **Chapter 6**, therefore, sub-phase A of the design synthesis phase focused on developing the decision support tool – the CVSIT, to assist with the effective and efficient reporting of ADRs within the environment of MPP drug provision systems. In this chapter, the dimensions of the tool, its operations and the background logic are discussed.

In sub-phase B, which was discussed in **Chapter 7**, a validation process evaluated the applicability and the practicability of the tool. Two methods were used: (i) a case study was applied, and (ii) semi-structured interviews with SMEs were conducted. The aim of the first method was to evaluate applicability of the CVSIT in real world situations, and furthermore to determine if the tool could assist practically with the effective and efficient reporting of ADRs within the environment of MPP drug provision systems. In this regard, two retrospective case studies looked at the roll-out of Bedaquiline, a drug used for MDR-TB treatments in South Africa. Case A investigated how Bedaquiline had been made available in a cohort format, while Case B focused on the country-wide roll-out of Bedaquiline in South Africa. The relevant background information related to these two cases was provided, and the findings with respect to the application of the CVSIT were discussed. The second method, conducting semi-structured interviews was aimed at evaluating the applicability, and practicability of the tool and to determine if the tool adds value to the effective and efficient reporting of ADRs. This process, the results of the interviews and the subsequent adaptations made to the CVSIT, were discussed in that chapter. It concluded by presenting some closing remarks about the CVSIT validation process.

8.2 CONTRIBUTION TO THE PHARMACOVIGILANCE INDUSTRY

During this research study, it was established that, in the current healthcare landscape more innovative forms of drug manufacturing and distribution, such as the MPP, are becoming prevalent. However, these are challenging the traditional methods of drug safety monitoring and PV. The environments defined as the MPP drug provision systems pose distinctive challenges that call for a more context-specific PV system. Thus, this research sought to address this by developing a decision support tool that facilitates the development of context-specific PV systems within the context the MPP.

In this research investigation, four niche factors, namely, (i) traditional PV systems, (ii) MPP, (iii) HIV, TB and Hepatitis C, and (iv) RLS were all taken into account when developing this decision support tool. Furthermore, in order for the Vigilance System to address the challenges posed by these factors, a so-called challenges landscape was developed to gain a systems level perspective and understanding of them. Known as the PVCCL, this landscape gives an overview of the different challenges faced throughout the entire pharmaceutical value chain, from drug manufacturing to ADR monitoring, that have to be taken into consideration when developing the proposed decision support tool. The PVCCL thus contributes to the field of pharmacovigilance, as it provides a synopsis of the challenges that are faced when considering these niche factors, and moreover indicates how these challenges influence the pharmaceutical value chain and subsequently the PV processes. The PVCCL further contributes to the pharmaceutical landscape as a whole, as it considers the entire pharmaceutical value chain and the unique challenges brought on by the niche factors within this context. Thus, the PVCCL can be seen as a foundational platform for research within the field of the pharmaceutical industry, specifically as it pertains to the niche factors.

Using the developed PVCCL, systematic literature reviews and verification processes, a requirement specification was developed that would guide the development of the decision support tool. This requirement specification in itself contributes to the PV industry, as it does not only address the minimum requirements of a PV systems (WHO and The Global Fund, 2010), but also the unique requirements of the niche factors within the context of the entire pharmaceutical value chain.

The aim of this research inquiry was to develop a context-specific PV system within the environment of MPP drug provision systems. Thus, the Vigilance System was proposed through the development of the Vigilance System Component – Intervention Index, which aids as a guideline for the implementation of a Vigilance System. This index contributes to the field of PV by providing a structure for the implementation of a Vigilance System that considers direct, supporting and additional components with subsequent intervention strategies. Furthermore, this index proposes that attention should be paid to those supporting components in the PV industry, that do not directly relate to the ADR reporting process and that are often disregarded in traditional PV systems.

The final outcome of the dissertation was to transform the Vigilance System Component – Intervention Index, an index that provides an overview of the various Vigilance System components and intervention strategies, into a decision support tool (the CVSIT) that would assist in the development/implementation of a Vigilance System. The CVSIT can be used to assess a specific drug provision project's profile (with respect to the drug being considered, the target patient group, and the resources available to the project) and subsequently to create a customised implementation plan for a Vigilance System that identifies the intervention strategies applicable to the specific project. The following attributes of the CVSIT were reaffirmed:

- i. The CVSIT is an all-encompassing tool that considers both direct and supporting components within a Vigilance System and provides a holistic systematic approach to the development of said system;

- i. The CVSIT should be used as an initial tool (or a first phase tool), when developing a Vigilance System, as it provides a guideline for an implementation strategy that could be investigated further;
- ii. The CVSIT can be used complementary with other PV related tools, such as a country's specific national PV guidelines, the WHO PV toolkit, and the IPAT, thus reaffirming that the roll-out of this tool will be supported within the healthcare landscape; and
- iii. The CVSIT is both robust and agile, as it can be used by various RLS countries and stakeholders, such as medicine regulatory authorities, pharmaceutical companies, health and drug launching programs, and other stakeholders involved with PV to improve ADR reporting within the context of MPP drug provision systems.

In conclusion, this research inquiry contributes to the pharmacovigilance industry and the pharmaceutical industry not only with the final research output, the CVSIT, but also by challenging the current traditional PV systems. The contribution of this research lies in providing systematic though processes for the development of a drug safety reporting system that considers innovative intervention strategies currently being overlooked.

8.3 ADDRESSING THE RESEARCH OBJECTIVES

The aim and objectives as set out in Chapter 1 have been met by this research study. The aim was to develop a tool that would assist pilot drug roll-out projects with implementing a Vigilance System, and this was achieved by developing the CVSIT. Table 8.1 gives an overview of the objectives and in which chapters and sections they were achieved.

Table 8.1: Research aim and objectives achieved

Research objectives	Chapter and section numbers
RO1 Review the literature pertaining to the factors of (i) traditional PV systems, (ii) the MPP, (iii) the disease burden associated with the MPP (HIV, TB and Hepatitis C), and (iv) RLS, in order to contextualise the research problem under consideration, namely, the fact that traditional PV systems are inadequate in supporting the unique needs and challenges brought on by these factors.	Chapter 2, Section 2.2 & Chapter 3, Section 3.1
RO2 Develop a challenges landscape related to the factors of (i) traditional PV systems, (ii) the MPP, (iii) HIV, TB and Hepatitis C, and (iv) RLS in order to gain an understanding of what challenges a context-specific PV system will have to address.	
RO2.1 Conduct systematic literature reviews to identify the challenges associated with each of the factors as stated above.	Chapter 2, Section 2.3 & Chapter 3, Section 3.2
RO2.2 Identify and define possible relationships between the identified challenges and the pharmaceutical value chain.	Chapter 2, Section 2.4.2 & Chapter 3, Section 3.4.2
RO2.3 Synthesise the challenges and the identified relationships to develop a challenges landscape that will support the development of a proposed context-specific PV system.	Chapter 3, Section 3.5

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Research objectives	Chapter and section numbers
RO3 Develop a requirements specification that will guide the development of a decision support tool, drawing on the findings from RO1 and RO2.	
RO3.1 Conduct systematic literature reviews pertaining to (i) traditional PV systems, (ii) the MPP, (iii) HIV, TB and Hepatitis C, and (d) RLS, to identify any additional requirements that these factors would call for	Chapter 4, Section 4.2
RO3.2 Consider the developed challenges landscape as described in RO2, with respect to the identified requirements specification; as per RO3.1, to determine if additional requirements should be considered	Chapter 4, Section 4.3
RO3.3 Synthesise the requirements identified in RO3.1 and RO3.2 to develop a combined requirements specification that will guide the development of a decision support tool	Chapter 4, Section 4.4
RO3.4 Conduct a verification process to authenticate the developed requirements specification as stated in RO3.3.	Chapter 4, Section 4.5
RO4 Develop a decision support tool that facilitates the development of a context-specific PV systems within the context of the MPP.	
RO4.1 Identify possible intervention strategies that would address the requirements specification as discussed in RO3	Chapter 5, Section 5.1
RO4.2 Synthesise the intervention strategies identified in RO4.1 to develop the foundational features of the decision support tool	Chapter 5, Section 5.2
RO4.3 Develop the detailed decision support tool	Chapter 6
RO4.4 Validate the developed decision support tool to evaluate the applicability and practicability of the developed tool	Chapter 7

8.4 LIMITATIONS

As this research inquiry investigated the niche setting of MPP drug provision systems, the outcomes are context-specific to these settings. Thus, the CVSIT was developed for the specific context of the niche factors, (i) traditional PV systems, (ii) MPP, (iii) HIV, TB and Hepatitis C, and (iv) RLS, which limits the operation of the tool.

8.5 FUTURE WORK

It is recommended that the following opportunities are explored as future research, as they build on the deliverables of this research investigation.

The first recommendation is that the developed tool, the CVSIT, be amended with regard to the consideration of three different cases. Firstly, the tool could be adapted by including national PV requirements according to the specific country's regulatory authority, i.e. the PV requirements mandated by SAPRHA for South Africa. During the CVSIT validation process, this recommendation was made, however it fell outside the scope of this study, as the aim was to develop a robust tool that would be applicable to various environments within the MPP drug

provision systems – and thus not limited by a specific country’s PV requirements. Thus, it is recommended that future investigations look at incorporating national PV guidelines, and how this would affect the operation and usability of the tool.

During the CVSIT validation process, it was also established that the tool is not universal to all PV related project; however, it must be borne in mind that the tool was developed to assist specifically with the effective and efficient reporting of drug provision projects within the context of the MPP drug provision systems and that it is thus context-specific to these environments. However, it was also established that it can be applied to different environments if adaptations are made. Thus, it is recommended that future opportunities should explore the gaps in the tool when considering projects outside the present context, and identify opportunities to improve the CVSIT in these aspects. Furthermore, it is also proposed to follow a similar systematic thought process to investigate the development of an alternative, context-specific PV system within the context of other environments, for instance by considering other disease burdens.

Furthermore, the CVSIT offers a customised implementation strategy for a Vigilance System, with intervention strategies that are most appropriate and most suitable for a specific drug provision project. However, the CVSIT is only subsequent to the *identification* of such intervention strategies, and thus the financial, technical and operational feasibility of the intervention strategies should be pursued. This is an opportunity for future research to build on the CVSIT by identifying what further feasibility studies, i.e. financial, technical and operational, should be considered and conducted once a vigilance implementation plan has been developed for a specific project.

During the validation process, a number of tools were identified that could be used to complement the CVSIT, such as the WHO PV toolkit, and the IPAT. To verify these findings, it is recommended that additional investigations should be conducted on the complementary use of these tools in real world situations by looking at additional case studies. Furthermore, it was confirmed during the validation process that a case study related to an existing drug project in the context of MPP drug provision systems should be looked at in order to truly validate the usability of the CVSIT in a real-world situation.

In this research inquiry, a system engineering approach was used to develop a context-specific PV system, namely the Vigilance System, for the niche environment of MPP drug provision systems. This systematic approach addressed the needs of this specific environment and developed systems solution to address the challenges faced within these settings. The MPP drug provision systems represented an environment where factors such as the MPP, RLS and disease burden associated with the MPP (HIV, TB and Hepatitis C) had to be taken into consideration, and thus the tool is ideally developed for these environments; however, it is not exclusively applicable to these environments. Future investigations could thus verify the use of the CVSIT in other environments of different illnesses, patient groups and resources, for instance.

8.6 CHAPTER 8 CONCLUSION

This chapter concludes this research inquiry, which investigated the absence of adequate PV systems within the context of MPP drug provision systems and addressed this by a context-

specific PV system – a Vigilance System that considers the relevant niche factors within this particular environment. In this chapter, an overview of the research was provided, and it discussed how the aim and objectives were achieved. The contributions made to the research were also included as well as suggestions for possible future work that could build on the findings of this research inquiry.

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Appendix A. Research outputs

In this appendix the articles that have been written and published during the course of this research inquiry is included. The first document is titled “*Developing a challenges landscape relating to drug safety, provision, and distribution in resource-limited settings for the case of HIV/AIDS*” and is published in the South African Journal of Industrial Engineering Volume 9, addition 3.

The second document is titled “The case for a niche pharmacovigilance system relating to drug provision and distribution in resource limited settings “and can be found in the ICE conference proceedings in the IEEE Xplore Library.

The following sections are included:

A1: Article 1 - Developing a challenges landscape relating to drug safety, provision, and distribution in resource-limited settings for the case of HIV/AIDS

A2: Article 2 - The case for a niche pharmacovigilance system relating to drug provision and distribution in resource limited settings

A.1. Article 1 - Developing a challenges landscape relating to drug safety, provision, and distribution in resource-limited settings for the case of HIV/AIDS

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DEVELOPING A CHALLENGES LANDSCAPE RELATING TO DRUG SAFETY, PROVISION, AND DISTRIBUTION IN RESOURCE-LIMITED SETTINGS FOR THE CASE OF HIV/AIDS

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ABSTRACT

Since 2010, pharmaceutical organisations have begun to provide drug patents in sub-Saharan Africa through the UN Medicine Patent Pool. This initiative allows any pharmaceutical manufacturer to access these patents and manufacture the drugs, thereby aiming to decrease the associated lead times and costs. The participation of numerous manufacturers, some of whom may not have well-established quality control systems in the market, intensifies the need for effective drug quality monitoring. Research indicates that it is often the case that these 'niche drug provision systems' face many challenges with the quality of new-generation drugs and the implementation of effective pharmacovigilance (PV)¹ systems for the reporting of adverse drug reactions. The lack of resource efficiency in adverse drug reaction reporting within the sub-Saharan context is also a growing concern.

OPSOMMING

Sedert 2010 het farmaseutiese organisasies deur middel van die *UN Medicine Patent Pool* medisyne patente vrygestel vir lae- en middelinkomste lande. Hierdie inisiatief laat toe dat enige farmaseutiese vervaardiger die patente kan gebruik om medisyne te vervaardig; sodoende word die koste en vervaardigingstyd verminder. Aangesien 'n aantal verskillende vervaardigers, waarvan sommige nie goed gevestigde kwaliteit stelsels het nie, kan deelneem, moet daar goeie 'pharmacovigilance' (PV) toegepas word. Navorsing dui egter daarop dat dit dikwels die geval is dat hierdie plaaslike medisyne vervaardigers baie uitdagings ervaar in verband met medisyne voorsiening wat weer effektiewe PV-stelsels impliseer. Die gebrek aan menslike hulpbronne vir die monitering van negatiewe reaksies op die medisyne in hierdie lande is ook 'n groeiende probleem.

1 INTRODUCTION

In the contemporary landscape it is evident that there has been a significant shift in health care trends around the world that calls for innovative drug manufacturing, distribution, and surveillance monitoring. According to Rohrbach [1], the growing demand for healthcare — combined with the switch in focus from treatment to prevention — has placed pharmaceutical companies under pressure from governments and consumers to reduce their prices and improve the value of their therapies. However, other stakeholders, such as the World Health Organization, also contribute to this pressure. The epidemic of communicable diseases in low- and middle-income countries adds to the pressure that pharmaceutical companies experience from stakeholders to ensure an affordable drug supply. According to the World Health Organization, in 2016 36.7 million people were living with

¹ In this article, 'PV' means 'pharmacovigilance' which refers to the science and application of the detection, assessment, and monitoring of adverse drug reactions after drugs have been licensed for use.

HIV/AIDS, the majority of whom lived in low-middle income countries [2]. These factors, combined with strict drug patent laws, make the affordable supply of drugs in these countries problematic [3].

Thus in 2010 the UNITAID medicine patent pool (MPP)² was established to improve access to the treatment of HIV, tuberculosis (TB), and hepatitis C by allowing access to specific drug patents [4], [5]. This innovation has played a significant role in addressing the HIV/AIDS epidemic from the perspective of access to medicine, as between 2005 and 2016 the proportion of patients receiving treatment increased from 6.9% to 53% globally [2]. However, the MPP has given rise to other challenges [6]. As multiple drug manufacturers are allowed to access the drug patents, quality monitoring in these settings has to be very well-established. Such challenges are often attributed to inadequate local drug manufacturing and distribution systems [6].

However, when aiming to address specific challenges brought about by an intervention, as is the case with those arising from the MPP allowing any drug manufacturers access to patents, the context within which such a system exists has also to be considered. As mentioned earlier, the MPP only allows access to patents in low- and middle-income countries, which often have only limited resources. One example of limited resources in the sub-Saharan African region is the deficit of 24.8 million doctors and nurses, resulting in 2.3 healthcare workers per 1000 people in Africa. This is 90% less than in the United States of America, where there are 24.8 healthcare workers per 1000 people [7]. In addition to the limited human resources in these countries, funding and opportunities for research and development are also limited [8]. Thus, when considering the challenges that arise through the implementation of the MPP, the context of limited resources should also be considered.

These challenges in drug manufacturing and distribution in the context of resource-limited settings call for an effective, well-established drug monitoring and pharmacovigilance (PV)³ system to assist in improving patient safety. In order to develop such a PV system that will support, facilitate, and improve additional challenges brought on by inadequate drug manufacturing and distribution, the challenges need to be identified and understood to ensure that such a PV system overcomes them and does not give rise to any additional ones. It is also recognised that the current PV systems do not adequately support the unique MPP practices. This highlights the need for a PV system to support the unique needs of drug monitoring in such a setting, and to provide evidence that warrants the deployment of a PV system to support effective drug monitoring. In order to develop the characteristics of such a 'niche PV system'⁴, a requirement specification will have to be developed. This requirement specification will be based partly on the insights gained from evaluating the challenges and incorporating best practices, current PV requirements, and the ability of the PV system to function in such a setting. A niche PV system can then be designed either by transforming the traditional PV system or by transitioning to a new PV system using the developed requirement specification.

This paper, however, will focus on the challenges posed by drug manufacturing and distribution systems within resource-limited settings, which will be incorporated into the requirement specification for PV systems for such a setting. These challenges will be identified by conducting a systematic review, after which they will be arranged into a challenges landscape to understand the system perspective. Due to the high prevalence of HIV in South Africa, this research inquiry will consider challenges that arise with the roll-out of antiretrovirals (ARVs) [2].

2 CONTEXTUALISATION: MPP DRUG SAFETY, MANUFACTURING, AND DISTRIBUTION IN RESOURCE-LIMITED SETTINGS

Due to the growing number of HIV/AIDS patients without treatment in low- and middle-income countries, it was evident that an innovative way to provide antiretroviral treatment (ART) had to be

² MPP is an initiative which allows any manufacturer to access the available patents and manufacture drugs; thereby aiming to decrease lead time and costs associated with these drugs.

³ 'Pharmacovigilance' is defined as the science and application of the detection, assessment, and monitoring of adverse drug reactions after drugs have been licensed for use.

⁴ In this research inquiry, 'niche PV system' refers to a PV system that is designed for a specific population, implying a specific region and a specific drug. Such a PV system will most likely operate and be managed differently from 'traditional' PV systems.

implemented [2], [3]. One of the reasons that very few HIV/AIDS patients did not receive treatment was the high prices for treatment caused by the patent system, in which a company had the monopoly over a particular drug. ARVs also have to be taken in combination with other drugs, each with their own patent; and this also resulted in very high prices [3].

Thus, in 2010 the MPP was established by UNITAID to increase access to treatments for specific communicable diseases such as HIV, hepatitis C, and TB in low- and middle-income countries through sharing technologies and patents [4]. A patent pool is defined as a collaboration between patent holders and other third parties, where licences are offered for use in exchange for a fixed price or royalties. The implementation of a medicine patent pool makes the production and distribution of drugs accessible to a broader population at a faster rate and at more affordable prices [3]. The WHO assist the MPP by prioritising the medicines that were required, and patent holders voluntarily agreed to license their medicines to the MPP, which in turn issued generic pharmaceutical companies with licence rights to manufacture these medicines.

The implementation of MPP has many advantages, such as facilitating competition, improving low-cost manufacturing, and encouraging research and development (R&D) [3], [9]-[11]. Through the implementation of the MPP, competition is facilitated because multiple drug manufacturing companies can access the same patents. As competition between manufacturers increases, drug prices drop, making drugs more affordable [9]. Through the MPP, low-cost manufacturing companies are also able to approach the patent pool to negotiate licensing agreements to create generic versions of these drugs [3]. As mentioned earlier, antiretroviral drugs need to be taken in combination with other drugs in order to be effective [3]. However, the patent pool encourages R&D and innovation for the treatment of HIV/AIDS, as the patents for the drugs are accessible and can be used for new fixed-dosage combinations [3], [10]. The manufacturing companies are given the flexibility to develop new and appropriate formulations and fixed-dosage combinations to meet the specific needs of patients. Often the drugs are not adapted for use in developing countries – as in the case of paediatric treatments, as virtually no children are affected by HIV/AIDS in developed countries [9]-[11].

However, certain challenges arise when considering the provision of access to medicine through the MPP, such as local manufacturing, distribution, R&D, sub-standard medicines, and other regulatory issues [6]. The patents are available to any drug manufacturing companies in low- and middle-income countries that wish to make use of them; and although the manufacturers need to meet certain quality standards, it is often difficult to monitor the quality process of these drugs. Research found that, although the MPP does not directly cause any difficulties, the drug manufacturing and distribution system in these settings, made possible through the MPP, produces numerous challenges [12], [8].

In section 3, the different challenges that arise due to inadequate manufacturing and distribution systems in resource-limited settings will be identified through a systematic review, after which they will be discussed before developing a challenges landscape.

3 CHALLENGES POSED BY DRUG MANUFACTURING, DELIVERY, AND RESOURCE-LIMITED SETTINGS

As previously mentioned, the challenges that arise in the manufacturing and distribution of drugs for which patents are made available through the MPP can be attributed to inadequate drug manufacturing and distribution systems [6], [12]. These challenges affect patient safety, and so need to be addressed to ensure that the necessary monitoring systems are in place. The low- and middle-income countries that access the MPP also often have limited resources, which further complicates the challenges [7].

In this section, the aim is to identify the challenges arising from drug manufacturing and distribution systems in resource-limited settings in developing countries. Once these challenges have been identified through a systematic review, a challenges landscape can be developed to indicate the system perspective, which will contribute to the development of the requirement specification for a PV system in these settings.

First the approach to, and the results of, the systematic review will be given, after which the different challenges will be defined.

3.1 Approach

Due to the great extent of the available literature on drug manufacturing and distribution, a systematic review was conducted to limit the review and ensure that a significant amount of research into the challenges in this landscape could be included. The academic database Scopus—the largest abstract and citation database of peer-reviewed literature⁵—was used to conduct the primary search protocol. In addition, since the use of keywords in a search protocol is most effective in Scopus, and other databases often deliver irrelevant documents when using this search technique, Scopus was deemed a suitable platform for this research inquiry. However, given the focus on healthcare environments, databases such as PubMed were used for informal search methods, and serendipitous findings were included in the research. Using Scopus, a total of 1870 relevant articles were found using specific key words and phrases (Table 1). In order to find the most relevant documents, a set of different criteria points were included in the search protocol. These criteria points included only documents from 2010 and onwards, as the MPP was only introduced in 2010. Furthermore, documents that were not originally published in English but had been translated, and any duplicate documents, were excluded. The remaining documents' titles and abstracts were then screened for relevance. Documents concerned with relevant topics, such as the challenges posed by drug manufacturing or distribution systems or settings with limited resources regarding HIV/AIDS, were included in the final set. In the end, a total of 41 relevant documents were found from Scopus and seven from PubMed. These were reviewed and used to identify the challenges that are experienced in the context of drug manufacturing and distribution systems in resource-limited settings.

The process that was followed to limit the number of documents can be found in Figure 1.

Table 1: List of search terms used in systematic review

Index	Search terms	Number of articles	Number after 2010
1	Drug Manufacturing	480	257
2	Drug Manufacturing & Challenges	45	31
3	Drug Manufacturing & HIV	4	1
4	Drug Manufacturing & Developing Countries	16	8
5	Drug Manufacturing & HIV & Challenges	1	1
6	Drug Manufacturing & Challenges & Developing Countries	3	1
7	Drug Manufacturing & Quality	188	102
9	Drug Distributions & Challenges & HIV	232	147
10	Drug Distributions & Challenges & Developing Countries	14	7
11	Drug Resistance & HIV & Developing Countries	352	189
12	Counterfeit drugs & Developing Countries	126	84
13	Resource Limited Settings & Challenges & HIV	337	257
14	Resource Limited Settings & Challenges & developing countries	144	123
15	Patient safety & HIV & Developing Countries	24	17
16	Drug Packaging & Challenges & HIV	10	5
17	Drug Packaging & Challenges & Developing Countries	9	8
18	Adverse Drug Reactions & Drug Manufacturing	58	29
19	Adverse Drug Reactions & HIV & Developing countries	84	64

⁵ <https://www.elsevier.com/solutions/scopus>

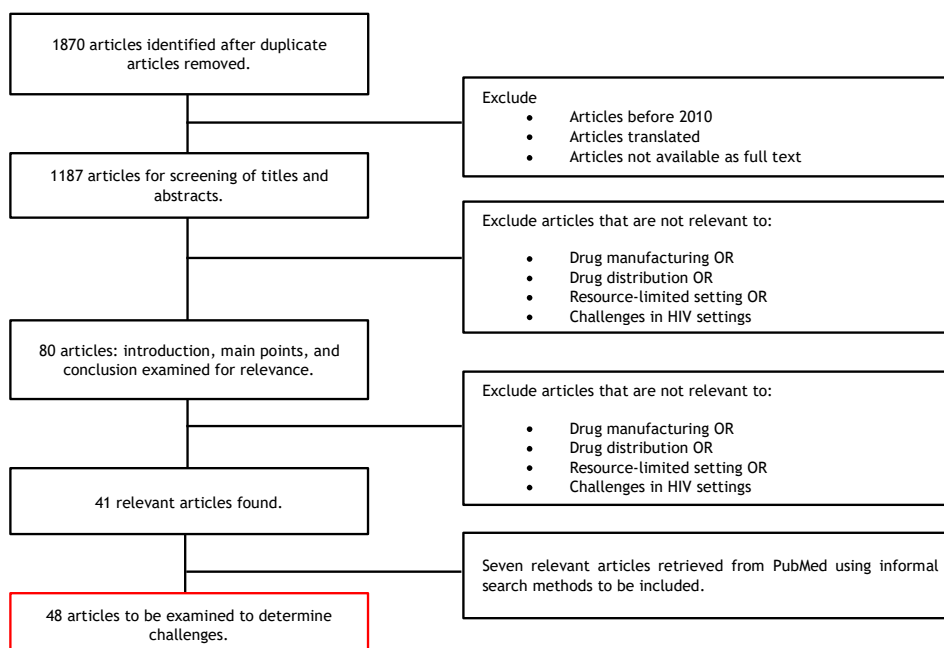


Figure 1: Process of systematic review

3.2 Results

Once the systematic review had been completed, the different challenges posed by inadequate drug manufacturing and distribution systems, and the challenges posed by limited resources, could be identified and listed. From the literature the following 19 factors were identified:

- Drug dosages
- Labelling & packaging
- Specialised drugs
- Traditional medicines
- Paediatric drugs
- Drug resistance
- Drug quality
- Counterfeit drugs
- Substandard drugs
- Record-keeping
- Adverse drug reactions (ADR)
- Drug-drug interactions
- Drug adherence
- Drug supply
- Drug shortages
- Drug stock-outs
- Late ART initiation
- Lack of safety reporting
- Integrity of system

Table 2: Overview of occurrences in systematic review

Occurrences of challenges in systematic review															
Date	Drug Manufacturing					Combination of distribution and RLS			Combination of manufacturing, distribution and RLS						
	Dosages	Paediatric drugs	Specialised drugs	Traditional medicine	Labelling	Drug supply	Drug stock-outs	Drug shortages	ADR	Drug adherence	Quality	Counterfeit drugs	Drug-drug interactions	Substandard drugs	Drug resistance
2010				XX		XX	X		XX	XX	XX			X	
2011	X	X	X			XX	X	X	XX	XX	X				X
2012						XX			XX	X		X			
2013	X				X	X	X		X	X	X	X	XX	X	XX
2014						X			XXX	XXX	X	X		X	
2015			X						X	X	X			X	
2016	X	X	X					X	XXXX	X	X		X		
2017		X		X	X						X	X			
Total	3	3	3	3	2	4	3	2	13	9	8	4	4	4	3

Each X represents a document

From the data provided in Table 2, a number of trends seem to emerge, as some challenges are only mentioned in more recent years. For example, labelling, specialised drugs, drug-to-drug interactions, and lack of reporting have appeared in the more recent literature, while challenges

such as drug shortages and drug resistance have not appeared in the literature in recent years. From Table 2 it can also be seen that certain challenges have occurred more constantly over the last eight years, such as ADR and quality challenges.

3.3 Defining challenges

The 19 factors that were identified in the systematic review have a specific impact on the pharmaceutical and healthcare systems. These challenges are defined and explained in the next sub-section.

3.3.1 Adverse drug reactions

According to the WHO, an ADR is defined as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function” [13]. ADRs can affect the treatment process and have negative effects on patients’ quality of life, especially for HIV-infected patients on ART. Serious ADR often causes patients to stop taking drugs, leading to a lack of drug adherence or to treatment failure, which negatively impacts patients and society. ADRs are also often a cause of re-admission to a hospital, aggravating the health care burden in resource-limited settings [14]-[19]. It has also been shown that ADRs have been found to be preventable, justifying the need to improve pharmacovigilance. The early detection of ADRs is also pivotal when ensuring the sustainability and optimisation of a treatment process. However, it has been reported that detection, especially in paediatric treatments, is difficult [20]. Furthermore, through the MPP, multiple drug manufacturers are able to produce generic drugs and new fixed-dosage combinations, making it critical that ADRs in HIV patients are monitored carefully [14], [18], [19].

3.3.2 Drug adherence

‘Drug adherence’ refers to patients keeping to the recommendations made for the dosage, timing, and frequency of taking their medication. With regard to ART, it is said that 95% drug adherence is required to ensure that patients do not develop resistance or suffer from treatment failure [21]. From the literature consulted, it has been determined that non-adherence in ART is caused by a range of different factors; but one of the main causes is ADR [17], [18], [22]. However, studies in developing countries have also indicated that other factors contribute to non-adherence, such as dissatisfaction with the healthcare system, perceived stigmas, distance to ART clinics, limited social support, poor record-keeping, the attitude of healthcare workers, and certain personal factors [23], [17], [21]. Studies do indicate, however, that adherence can be improved with peer counselling and education [24].

3.3.3 Quality

Ensuring that the drugs that patients take are safe and effective is one of the priorities of the pharmaceutical industry, and it needs to be continuously addressed throughout the process. Many different aspects, such as good manufacturing practices, quality monitoring, and drug plant characteristics contribute to low-quality drugs. It has been found that, in low income countries, the quality of drugs is often inconsistent; thus proper quality control should be assessed more often, especially when new drug manufacturers are used [25]-[27]. Another aspect to consider when addressing drug quality is the production of generic drugs, which is promoted through the MPP. Generic drug manufacturing and the production of fixed-dosage combinations challenge the existing system, as the different areas of responsibility are misunderstood [28], [23].

3.3.4 Lack of reporting

Limited human resources in developing countries contribute to the lack of reporting of ADRs, especially in public HIV healthcare systems. Most low- and middle-income countries have inadequate legislation for mandatory reporting by health care professionals [29], [30], [31]. Furthermore, it has been found that the severity and preventability of ADRs are often under-reported in developing countries, possibly due to inadequate healthcare resources and knowledge among healthcare workers in these regions [14].

3.3.5 Record-keeping

Medical health records are essential to health care providers, as they contain specific information about a patient, such as their unique patient identifiers and medical history. Medical health records contain vital information about a patient’s health, and are needed for their current and future treatment. Health care providers are required to write up health records so that the information is available when the patient returns to a health care facility [32], [33]. However, it is often the case

in developing countries that effective record-keeping is a challenge [31], [34]. Healthcare providers mention that patients' records are often lost, resulting in the loss of all previous data, and sometimes even leading to certain medical procedures being repeated [21]. This therefore underpins the need for effective record-keeping systems, such as electronic health records.

3.3.6 Counterfeit drugs

The WHO describes counterfeit or falsified drugs as “medical products that deliberately/fraudulently misrepresent their identity, composition or source” [35]. The WHO also states that counterfeit drugs can be branded or generic drugs that contain the incorrect ingredients, or none at all, or inadequate amounts of active ingredients, or that are falsely packaged [36]. The health of patients who receive counterfeit drugs is threatened, as they are at risk of developing ADR or drug resistance [23], [27], [28], [37]. Counterfeit drugs are often a concern in areas where there is a shortage of drugs, or drug manufacturing and distribution systems are not registered [23], [38].

3.3.7 Drug-drug Interactions

The interaction between ARVs and other drugs is often harmful to a patient's treatment procedure. ARVs are often co-administered with antitubercular medication; however, this often leads to a higher frequency of drug-induced liver incidents and peripheral neuropathy. Thus TB/HIV co-infected patients' treatment should be managed more carefully. ‘Drug-drug interaction’ is defined as a change in the effect of the drug when it is taken together with another drug, and it can often lead to ADR [39]. The use of traditional medicines has also given rise to challenges in drug-drug interactions [23].

3.3.8 Drug supply

In developing countries, drug supply has often been a concern, especially for illnesses such as TB and HIV/AIDS, whose treatment requires a strict regime to be effective. Furthermore, when limited amounts of ART are available, ethical issues often arise about how the medication should be prioritised for different patients [23]. Delays in drug delivery in resource-limited settings are often caused by poor infrastructure such as poor roads and by financial burdens such as a lack of funding for fuel [37], [40]. The challenges posed by poor drug supply involve all aspects of the supply chain, from ordering systems to the storage and distribution of drugs. Case studies on weak ARV supplies in South Africa found that they were often caused by poor communication between provincial districts and facilities or between the consumer and the facilities. Studies have shown that supply systems that rely on consumer ordering affect shortages [41].

3.3.9 Late ART initiation

From the literature it has become evident that the need to ensure that people start their treatment during the early phases of the disease is just as important as ensuring that patients receive treatment [42]. Although there is no clear definition of just when it is ‘late’ for a patient to start ART, it can be deduced that it is when a patient's CD4 count is very low ($CD4 < 50$ cells/ μ L). Patients who initiate late ART have a higher risk of opportunistic infections than patients who start treatment at a higher CD4 count, with TB being the most common illness [43], [44]. From previous studies, the causes of late ART initiation can be grouped into health system-related issues, socio-economic obstacles, or inappropriate treatment criteria [44].

3.3.10 Substandard drugs

The WHO defines substandard drugs as “authorized medical products that fail to meet either their quality standards or specifications, or both” [35]. A drug is thus regarded as a substandard drug if it contains too many or too few active ingredients in comparison with the formulation specifications. However, there have been substandard drugs that were toxic in nature or that contained fatal levels of toxic ingredients. Substandard drugs are often found in poorer settings with manufacturing and distribution systems that use unqualified personnel and inadequate control systems. Substandard drugs are more frequently found, and pose a greater threat to patients than counterfeit drugs [27], [36].

3.3.11 Dosages

Taking the correct dosage when on ART is important, since taking an incorrect dosage leads to there being an inadequate amount of the drugs to fight the virus. Often, when tablets are split, asymmetry results in an unproportioned dosage of the ARV drugs. Furthermore, it cannot be assumed that the ingredients are evenly distributed in a tablet; thus pill splitting is not recommended [45].

3.3.12 Drug resistance

Drug resistance is when the response to a drug in a susceptible parasite population decreases significantly [46]. According to studies by the WHO, it was found that in 2010 the prevalence of HIV drug resistance for patients starting treatment was 6.8% for any drug, and that the treatment of these patients was more likely to fail [47], [48]. Drug resistance leads to further challenges relating not only to the patient's own future treatment, but also to the whole community [25].

3.3.13 Drug stock-outs

The WHO defines a drug stock-out as the total absence of a medication that has been identified as essential at the point of service delivery [49]. Drug stock-outs are often the result of poor infrastructure and insufficient human resources [40], [50]. Although alternative ARTs are often provided in the case of a stock-out, it still poses the threat of drug resistance, as it might cause suboptimal drug levels [34]. It has been reported that one-third of countries worldwide struggle with drug stock-outs, thus increasing the risk of treatment failure and failed drug adherence [30], [34], [51]. To ensure that stock-outs do not occur, it is critical that ART programme planning and rational forecasting processes are in place [30].

3.3.14 Paediatric drugs

The need for paediatric antiretroviral drugs is much higher in low- to middle-income countries, as developed countries have significantly reduced the mother-to-infant HIV rate. Furthermore, the use of adult ART for children is seen as ineffective, as children absorb and metabolise drugs differently than do adults. Through the MPP, drug manufacturers in developing countries can develop innovative fixed-dosage combinations specifically for paediatric use. However, when developing paediatric drugs, the palatability, taste, size, dosages, formulation, and ease of handling or administration of the drugs should be considered [45], [52].

3.3.15 Specialised drugs

In developing countries, certain specialised drugs are manufactured to specific contextual criteria. Two examples of such drugs that occur in the HIV treatment context are paediatric antiretrovirals and the use of traditional medicines. This is often the case in countries that are part of the MPP, as the patents often only cater for a developed country's needs [53], [45].

3.3.16 Traditional medicines

Many cultural and social differences that further complicate HIV/AIDS treatment in developing countries need to be considered, one being the increasing production and use of traditional medicines [54]. The increased production of these medicines raises issues of quality control, although intercultural standards are being developed for traditional medicines. Aspects to consider in relation to quality control are the use of raw materials, the knowledge of the manufacturers, and the lack of general safety studies [55]-[57].

3.3.17 Drug shortages

A drug shortage is defined by the WHO as the insufficient supply of medication or health products to meet the public's and patients' needs [49]. The drugs that are often affected by shortages are produced by smaller generic companies with little redundant capacity, which complicates the situation with production problems [58]. Previous case studies showed that patients who were on a waiting list for ART often died due to drug shortages. However, drug shortages can be prevented if there are sufficient resources to inspect and approve new drugs and ensure the quality of drugs. It has also been predicted that reducing the number of reviews and speeding up inspections would help to avoid shortages [59].

3.3.18 Integrity of system

The support, integrity, and confidentiality of health care workers has been seen to have an impact on ART. From the literature it has been found that HIV patients' distrust of and dissatisfaction with the healthcare system can lead to serious problems such as late treatment initiation or poor drug adherence, which often result in drug resistance or treatment failure. Healthcare workers who are supportive will motivate patients to take their ARVs, and educate them about the consequences and benefits of keeping to the treatment programme [21], [44],[60]. A case study [44] revealed that HIV patients often do not seek treatment, as they know that the healthcare staff often discuss their status – which is a very sensitive topic – in public. The compassion and support of healthcare workers are important in ensuring that patients follow through with their treatment [25].

3.3.19 Labelling

Mislabelling drugs can have a severe impact on a patient's safety, and can be more harmful for them. According to the WHO, labelling on drugs needs to contain the names and amount of the active ingredients, the batch number from the manufacturer, the expiry date, the name and address of the manufacturer, any storage instructions, and directions for use. It is particularly important that the directions and guidelines for use are clearly indicated [61].

4 CHALLENGES LANDSCAPE

As previously mentioned, the challenges that were identified in section 3 were found to relate to one another and to have an impact on one another. It was also established that challenges could have (possibly different) impacts on the various parts of the pharmaceutical value chain. Thus, an overview of the 'challenges landscape' is developed here to gain a holistic view of the challenges that face the drug manufacturing and distribution systems in relation to the provision of drug patents through the MPP. The challenges landscape will serve as a guide to determining any shortcomings in the traditional PV system by developing a requirement specification for a (niche) PV system that will support effective and efficient drug surveillance and monitoring. However, the development of the requirement specification falls outside of the scope of this paper; the key focus of this paper is, as mentioned earlier, to develop a challenges landscape to understand the system perspective in these settings.

The pharmaceutical value chain framework used for the purpose of this study has four sections: supply, distribution, product, and health system [62]. The 'supply' section is then sub-divided into 'drug development' and 'manufacturing', while the 'health system' section is split into 'patient usage' and 'monitoring systems' [62].

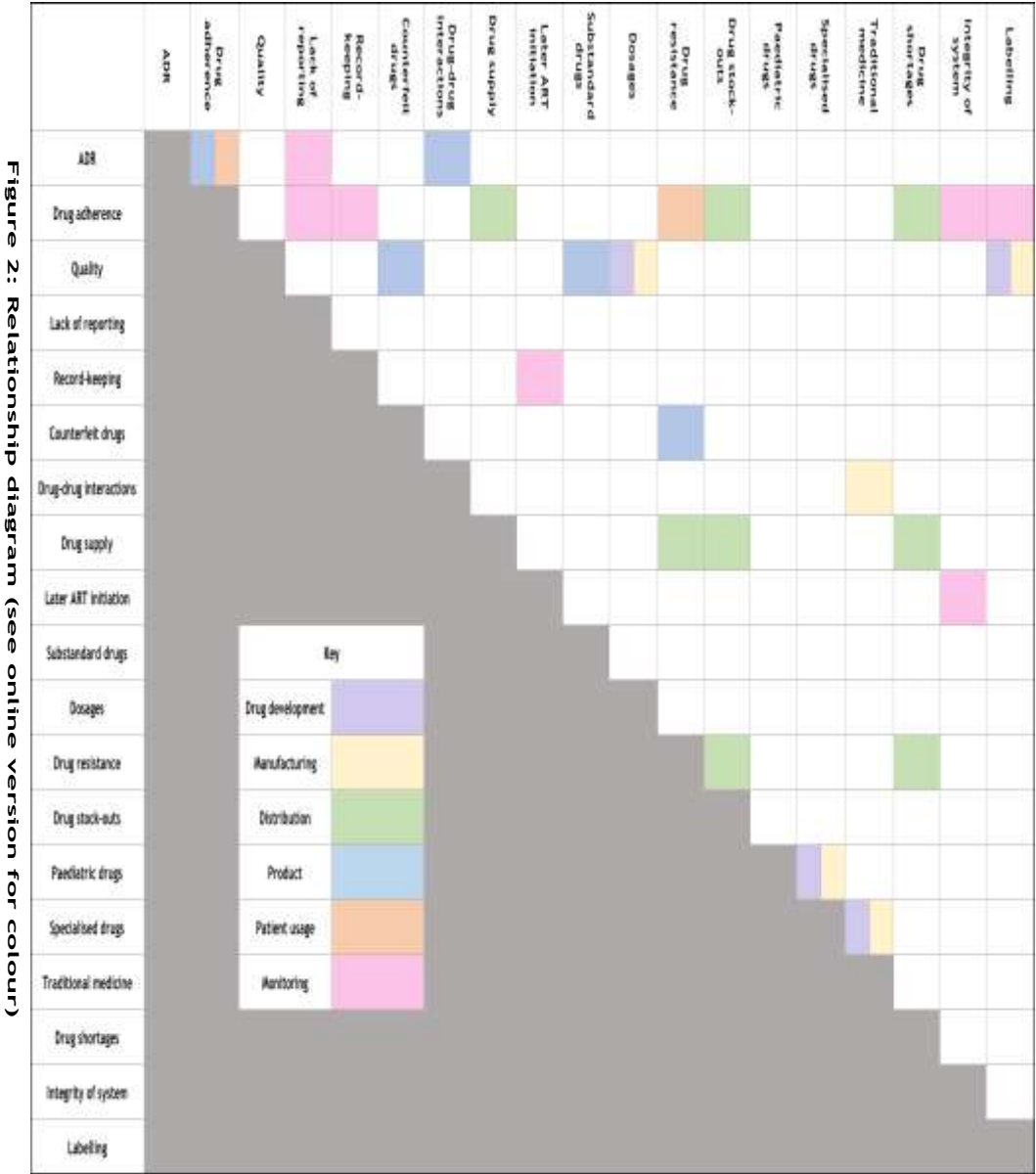
The challenges landscape, as discussed in the sections that follow, is discussed from three perspectives: firstly, the relationships between the various challenges are considered and presented in a relationship diagram; secondly, the relationship diagram, the pharmaceutical value chain framework, and the various challenges are amalgamated and presented in a schematic representation of the challenges landscape; and thirdly, the linkages and groupings presented in the schematic representation of the challenges landscape are elaborated on.

4.1 Relationship diagram & schematic representation of the challenges landscape

In Figure 2 the respective relationships between the challenges are indicated. These relationships were not necessarily explicitly mentioned in the literature, but after synthesising the information gathered through the systematic literature review, certain correlations and relationships between the different challenges could be identified. The relationships indicated in Figure 2 are grouped so as to indicate the impact a relationship has on a specific section of the pharmaceutical value chain. These sections of the value chain are distinguished in the key provided in Figure 2. In the case where a relationship has an impact on more than one section, both are indicated. The relationship diagram was used as an aid to create the challenges landscape. Schematic representation of the challenges landscape

Using the relationship diagram in section 4.1 and the information from section 3, a challenges landscape (Figure 3) was developed to indicate the inter-relationships and impacts between the different challenges, and their relationships with the different stages of the pharmaceutical value chain.

As seen in the schematic representation, the pharmaceutical chain is subdivided into four sections: supply, distribution, product, and health system. The challenges are in three main groups, referred to as A1-A3. They are formed when considering the systematic review and the causes of the challenges – namely, drug manufacturing and distribution in resource-limited settings. A1 refers to challenges due to inadequate manufacturing and distribution systems; A2 to challenges due to quality issues in drug manufacturing and distribution; and A3 to challenges due to limited resources. These challenges are grouped in subsections within these main groups; these sub-groupings, C1-C8, are discussed in section 4.2.



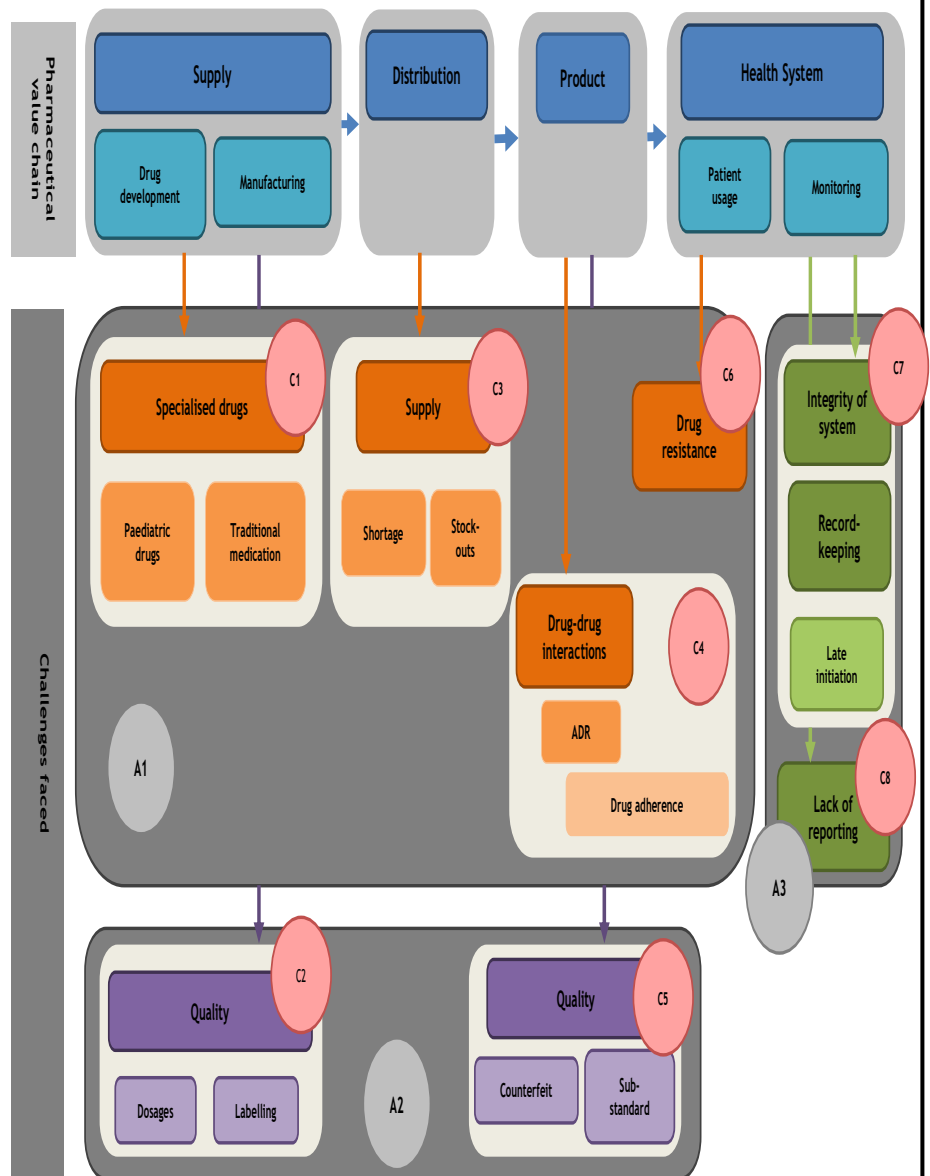


Figure 3: Challenges landscape (see online version for colour)

4.2 Links and groupings

As mentioned earlier, the different challenges have certain correlations, impacts, and/or relationships on or with each other, either directly or indirectly, which are illustrated by the challenges landscape in section 4.1. The explanation of the different groupings and relationships in the challenges landscape is provided in Table 3. It should be noted that the groupings and links between the different challenges were created with reference to the literature that was found through the systematic review and provided in section 3.

Table 3: Explanation of groupings of different challenges

Code	Value Chain	Grouping	Explanation
C1	Drug development and manufacturing	Specialised drugs, paediatric drugs, traditional medicines	In low- and middle-income countries, the development and manufacturing of drugs often requires the creation of drugs for specific needs of patients, referred to as 'specialised' drugs. In the case of HIV, the two specialised drugs that are most often found are paediatric drugs and traditional medicines [53], [45]. These challenges mostly appear in the phases of drug development and manufacturing. Furthermore, it is seen that traditional medicines often have an impact on drug-drug interactions [23].
C2	Drug development and manufacturing	Quality, dosages, labelling	The identified quality challenges have been shown to have an impact on the supply side of the value chain. Drug manufacturing companies have to have quality systems in place to ensure that the drugs they manufacture are safe and effective, and will not harm patients [26], [27]. Inadequate quality systems in drug manufacturing companies further complicate challenges such as drug dosage and labelling. If drug manufacturing companies do not have quality systems in place, the drugs dosages are often not adequate, as the ingredients are not distributed evenly [45]. The labels are often also incorrect. These challenges cause further problems with patient safety [61].
C3	Distribution	Drug supply, drug shortages, drug stock-outs	In the drug distribution part of the value chain, drug supply in low- and middle-income countries is one of the major concerns that is further affected by limited resources in these settings. As mentioned, many factors affect drug supply, from poor infrastructure to factors in the supply chain such as ordering systems [41]. The problems in drug supply create difficulties such as drug shortages and drug stock-outs. These lead to problems with patient safety, since shortages and stock-outs often are the causes of drug resistance in patients and poor adherence [34].
C4	Product, patient usage	Drug-drug interactions, ADR, drug adherence	Of the challenges that were identified, drug-drug interaction is one that arises in the final product stage of the value chain. As mentioned, ARVs often have to be taken in combination with other drugs, which can lead to negative drug-drug interactions. It has also been found that traditional medicines, which are often used in low- and middle-income countries, have an effect on drug-drug interactions [23]. Drug-drug interactions often also cause serious side effects and ADRs [39]. As previously mentioned, ADRs often have an effect on a patient's treatment process, as serious ADRs can impact a patient's adherence to the treatment, since they often stop taking their medications due to ADRs [21]. This inevitably affects not just the patient but the community as a whole. Drug adherence implicates the value chain in both the final product stage and the patient usage stage.
C5	Product	Quality, counterfeit drugs, sub-standard drugs	The quality of the final product is reduced by ineffective manufacturing and distributions systems [27], [28]. Drugs of inauspicious quality often lead to counterfeit drugs or sub-standard drugs. These challenges are mostly caused by a lack of quality in the drug supply process, and can seriously affect patient safety. Furthermore, counterfeit drugs often lead to serious ADR or drug resistance [23], [27], [28], [37].
C6	Patient usage	Drug resistance	Drug resistance is one of the challenges in the HIV setting that is associated with patient usage. Although drug resistance is not grouped together with other challenges, many factors impact on and lead to drug resistance. From the identified challenges, the biggest contributors to drug resistance are drug delivery, shortages, stock-outs, and poor drug adherence [34], [42]. Furthermore, drug resistance is complicated by inadequate drug monitoring systems, such as the low integrity of a health system and poor record-keeping [21], [44].
C7	Monitoring	Integrity of the health system, record-keeping system, late ART initiation	In monitoring – the final stage of the drug value chain – many challenges arise from limited resources. The poor integrity of the health care system and the lack of effective record-keeping are two of the contributing factors for late ART initiation. Late ART initiation can be very detrimental to patient care, and often leads to unnecessary deaths. Furthermore, the lack of effective record-keeping and dissatisfaction with the health care system affects drug adherence, which again leads to drug resistance [44].
C8	Monitoring	Lack of reporting	The lack of reporting during ART is one of the major challenges in resource-limited settings during the monitoring stage of the value chain. As mentioned, preventable ADRs have often been found to be under-reported, leading to further complications such as poor drug adherence and drug resistance [14].

4.3 The need to investigate the development of a niche PV system

Given the challenges landscape discussed above, the three perspectives – the relationships between the various challenges, the schematic representation of the challenges landscape, and the discussion on the linkages and groupings – lead to a comprehensive understanding of and insight into the challenges that arise from drug manufacturing and distribution systems that are related to the MPP

in settings with limited resources. From this challenges landscape, it is evident that there are shortcomings in the current (traditional) PV systems, as the challenges faced in these settings are not considered or incorporated when developing and designing the requirements and characteristics of a traditional PV system [63].

Thus, the challenges landscape highlights the need for an innovative PV system, such as a niche PV system, not only to support, facilitate, and improve the manufacturing and distribution of drugs and to address the challenges faced in these settings, but also to ensure that such a PV system will not create any additional problems or reinforce existing ones. The insights gained from the challenges landscape will assist with the development of a requirement specification for such a niche PV system that will address the current shortcomings in drug surveillance and monitoring in these settings.

5 CONCLUSION AND FURTHER RESEARCH

The challenges that arise in the manufacturing and distribution systems of drugs whose patents are made available through the MPP were discussed in this article. The challenges specifically related to developing countries, and challenges faced within the HIV/AIDS setting, were considered. It was determined that these challenges complicate different stages of the pharmaceutical value chain, and thus an innovative PV system is required to address these challenges.

The challenges landscape developed in this paper is a useful tool that indicates the relationships from a system perspective. Furthermore, the challenges landscape and the insights gained from it can be used in combination with other elements that relate to drug surveillance monitoring, such as best practices and current PV characteristics, to develop a requirement specification for an effective PV system in these settings.

In conclusion, this paper highlights the need for an innovative PV system, such as a niche PV system for a specific region and specific drug, to address and possibly eliminate the challenges that are faced in these settings, and to increase the effectiveness and efficiencies of such systems, given their unique characteristics. The insights gained from this paper will be considered when designing a niche PV system by transforming or transitioning from the traditional PV system.

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A.2. Article 2 - The case for a niche pharmacovigilance system relating to drug provision and distribution in resource limited settings

The case for a niche pharmacovigilance system relating to drug provision and distribution in resource limited settings

Presented by the development of a requirement specification

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In the contemporary healthcare landscape, the implementation of innovative drug manufacturing and distribution systems is becoming increasingly prominent in developing countries. One such platform is the Medicine Patent Pool (MPP) which grants multiple pharmaceutical manufacturers access to specific drug patents in order to manufacture these drugs. However, research suggests that these 'niche drug provision systems' often give rise to challenges which intensify the need for effective drug monitoring and pharmacovigilance (PV) systems that will support these practices of drug delivery. PV is defined as the practice of monitoring the effects of medical drugs after they have been licensed for use. This paper argues for the development and implementation of a 'niche PV system' that will support the unique needs presented by these practices; a requirement specification for such a PV system is thus presented.

Keywords — pharmacovigilance; MPP; requirement specification; challenges landscape; resource limited settings

I. INTRODUCTION

In the modern-day healthcare landscape, there has been significant changes within the pharmaceutical industry with regards to innovative drug manufacturing and distribution systems in developing countries. The key drivers of these changes were the unavailability of drugs (i.e. drug shortages and stock-outs) and the inaccessibility of affordable drugs in developing countries, often due to the high drug prices which are governed by the strict drug patent laws [1].

An innovation that aims to address the unavailability of, and inaccessibility to affordable drugs, is availing intellectual properties of drug patents made available through the Medicines Patent Pool (MPP) to pharmaceutical companies in developing countries [2]. The aim of the MPP is to increase the rate of manufacturing and decrease the prices of specific drugs, i.e. TB, HIV and Hepatitis C drugs, in an attempt to increase availability, and accessibility of affordable drugs to those who are affected [3]. The MPP allows for any pharmaceutical company to access these patents and develop generic versions of these drugs in an attempt to improve the availability, and access to affordable drugs [4].

This innovation has given rise to 'MPP drug provision systems' which refers to drug systems that consist of different practices in a pharmaceutical value chain, such as drug manufacturing, distribution, and quality monitoring within the context of the MPP. Furthermore, the MPP is often implemented in resource limited settings which face the challenge of having a limited amount of resources and funding available [5], [6], and thus when considering the context of these MPP drug provision systems, such challenges should be taken into account. It is suspected that by proposing the development of a 'niche PV system'¹, the challenges faced in the MPP drug provision systems will also be eliminated.

It is often the case that these MPP drug provision systems are deployed in areas that do not have effective drug monitoring systems, such as pharmacovigilance (PV), in place which creates additional challenges [7]. This – the drug provision system described above along with the related challenges – highlights the need to look at the incorporation of good manufacturing practice (GMP) and good distribution practices (GDP) when addressing these challenges. GMP is a quality system that aims to ensure that medical products are consistently produced to meet quality standards [8], whereas GDP is a quality assurance system that ensures the quality of medical products is maintained throughout all stages of the supply chain [9].

The World Health Organization (WHO) defines PV as, “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem” [10]. The challenges that arise from the MPP drug provision systems highlight the need to have an effective, well-established pharmacovigilance (PV) system in place to adequately support drug safety monitoring. However, it is recognised that the current PV systems are not equipped to adequately support these unique requirements [7]. Furthermore, it has been noted that the current PV systems face challenges that compromise the effectiveness of these drug monitoring systems and should thus also be taken

¹ In this article, 'niche PV system' refers to a PV system that is designed for a specific population, implying a specific region and a specific drug.

Such a PV system will most likely operate and be managed differently from 'traditional' PV systems [8].

into consideration when aiming to develop a niche PV system [11] given the context of the MPP.

In order to identify, define and ultimately develop such a niche PV system, a requirement specification that guides the development of the envisaged PV system has to be developed. However, before such a requirement specification can be developed it is important to understand the context of the environment that is being investigated, i.e. challenges associated with MPP and PV. This paper addresses the context of niche PV system by discussing the background and the challenges associated with the MPP drug provision systems and current PV systems. Subsequently, the process of developing the requirement specification as well as the core set of requirements for the niche PV system is discussed.

II. EXISTING THEORIES & PREVIOUS WORK

Before a requirement specification for the niche PV system can be developed, it is important to understand the context within which such a PV system will have to exist. In this section the focus is placed on providing background on the context of the pharmaceutical value chain which considers both the MPP drug provision systems and PV systems as well as the challenges that arise in these settings within the pharmaceutical value chain.

A. Pharmaceutical value chain

The pharmaceutical value chain has three main components, namely the manufacturing of the medicines, the final medical product and the distribution of the medicines [12]. However, it can be argued that drug safety monitoring, such as PV systems, should be included when considering the pharmaceutical value chain; as it has been found that these innovative modes of drug supply, such as the MPP, not only impact the manufacturing and distribution, but also the process of drug safety monitoring [9]. Thus, in the context of this paper, the pharmaceutical value chain is considered to have four key elements: supply, distribution, final product, and the health system which refers to the patient usage and drug safety monitoring [9], [12], [13].

B. The Medicine Patent Pool (MPP)

The MPP is a public health organisation that was launched in 2010 by UNITAID and aims to improve accessibility and development of life-saving drugs for HIV, TB, and Hepatitis C in developing countries through the sharing of technologies and patents [2]. The MPP collaborates closely with industry stakeholders and patent holders to develop licence agreements which allow pharmaceutical companies to manufacture generic versions of drugs, as well as with the WHO to prioritise these drugs for licensing [4]. Through this innovation, drugs are made available to a broader population at a faster rate [4].

In addition to having drugs provided to a broader population through the implementation of the MPP, there are additional advantages such as encouraging research and development (R&D), and facilitating competition [3], [14], [15]. Competition is assisted through the implementation of the

MPP as multiple pharmaceutical companies are allowed to access the drug patents and manufacture the drugs, which often results in a decrease in prices [3]. The pharmaceutical companies are also provided the flexibility to develop and adapt the drug formulations to create new fixed-dosage combinations to meet the specific needs for the area's population [9].

However, there are certain challenges that arise when considering the implementation of the MPP to improve availability and access to treatments. The MPP allows any pharmaceutical company in developing countries access to the drug patents, and although they have to meet certain quality standards, research shows that this has been difficult to monitor [9]. Though the MPP does not directly give rise to specific challenges, MPP drug provision systems do indirectly contribute towards challenges that impact the drug safety monitoring systems [9], [16], [17]. Thus, in the context of the pharmaceutical value chain it is important to understand the relationships and impacts of these challenges.

C. Pharmacovigilance (PV)

According to the WHO, the effective functioning of a PV system relies on data collection from health practitioners, and the systematic monitoring and analysis of the input data, especially in the case of new drugs that are rolled out. PV is aimed at improving patient safety with regards to medication but also to contribute to monitoring and assessing different drug reactions as well as the quality of drugs [18]. Furthermore, to ensure effective monitoring, PV should be a continuous process throughout the pre- and post-marketing authorisation phase of a drug [18]. With the roll-out of a new drug, an effective PV system is of paramount importance as all possible adverse drug reactions (ADRs)² should ideally be reported and investigated to ensure rapid detection and characterisation of drug risks. Additionally, PV systems continuously change and adapt to respond to certain requirements within a setting [18].

Numerous challenges exist with regards to drug safety monitoring, especially in developing countries [19]. From a study investigating the PV systems in South Africa, Uganda and India, it was found that barriers to effective drug monitoring include limited funding and a lack of training programmes [19]. With regards to the PV system in South Africa, research has established that, although legal requirements for drug safety monitoring are in place, challenges such as underreporting of ADRs, ineffective communication channels, and a culture of implementing PV tends to be lacking [18], [19].

Thus, when considering the development of the niche PV system that will address the challenges that the MPP drug provision systems contribute towards, 'traditional'³ challenges faced in PV system should also be considered.

² ADR is a response to a drug which is noxious and unintended, in a normal dosage for a specific treatment procedure [6].

³ Traditional challenges refer to the challenges that are faced in PV systems in the context of the pharmaceutical value chain, which are not directly brought on by the MPP.

III. METHODS

In this section the process, which was followed to determine the requirement specification, that outlines the foundational concepts from which the niche PV system can be developed, is described.

To ensure that the requirement specification for the niche PV system address the challenges that arise from the MPP drug provision systems and PV in the context of the pharmaceutical value chain a challenges landscape, referred to as the *pharmaceutical value chain challenges landscape*, was firstly developed based on insights gained from literature. The process of developing this challenges landscape and the final outcome of the landscape is discussed in this section.

The process of determining the requirements was threefold: the *pharmaceutical value chain challenges landscape* was consulted to determine what requirements these challenges call for in a PV system, a systematic review was conducted of literature pertaining to general requirements of a PV system; and the ability for such a PV system to work effectively in this environment of the MPP drug provision systems was considered.

Given that this research focuses on resource-limited settings and the inclusion of drug manufacturing and distribution, the requirement specification was developed with this focus in mind, and thus GMP & GDP were also taken into consideration. These practices were reviewed, and concepts were identified that could be incorporated into the set of requirements to improve the system and strengthen the function of the niche PV system (especially given the presence of the MPP). Furthermore, the literature also shows that many of the challenges that arise due to the inadequate drug manufacturing and distribution systems can be elevated through the implementation of these practices [20].

A. Pharmaceutical value chain challenges landscape

As mentioned, there are challenges that arise in the context of the pharmaceutical value chain due to flaws in the MPP drug provision system and current PV systems. It is thus important, when considering the development of the niche PV system, that such challenges are identified, understood and adequately addressed, to ensure that the proposed niche PV system can effectively support the unique requirements of these environments. In order to gain a holistic view of all these challenges, the *pharmaceutical value chain challenges landscape* was developed.

The *pharmaceutical value chain challenges landscape* is an expansion of the challenges landscape developed by Huysamen et al [6] which identified challenges associated with MPP drug provision systems. However, to address the traditional challenges faced in PV system a systematic review was conducted to identify the challenges which could be included to develop a challenges landscape that would address both MPP drug provision systems and 'traditional' PV systems. All the challenges identified were then examined to determine whether they relate to one another, as well as to determine the potential impacts and effects the different challenges might have on one another, and on the

pharmaceutical value chain. The challenges were grouped together based on their common characteristics and cause-and-effect relationships [6]. Seven main groups of challenges, referred to as 'challenges groups', were identified. Also, the impact that the challenges groups have on the different stages of the pharmaceutical value chain were identified. Both a schematic representation and a relationship diagram were developed for the *pharmaceutical value chain challenges landscape*, which can be found in Addendum A, Fig. 1 and Fig. 2.

The *pharmaceutical value chain challenges landscape* contains two dimensions. The first dimension is the pharmaceutical value chain with its' four key elements as explained in Section II, Subsection A. The second dimension is the main body of the challenges landscape that contain all the challenges identified during the systematic reviews in their respective groups; namely supply and distribution, quality, drug monitoring, PV culture, education, PV stakeholders, and ADR reporting. The landscape is arranged in such a way to clearly show how the challenges groups impact the pharmaceutical value chain at the different respective stages.

The understanding gained from the *pharmaceutical value chain challenges landscape* will contribute to the development of the requirement specification for the niche PV system.

B. Systematic literature on PV requirements

In order to gain a better view and understanding of the current PV system requirements that are documented, literature was consulted. The aim of this systematic literature review was to identify and gain a better understanding of the current PV requirements found in literature. Scopus and PubMed were used as the primary search databases. Using different keywords and phrases as indicated in Table I, relevant documents were identified. To ensure that only the most relevant documents were included, certain criteria points were used, such as only including documents that were published in English and from 2000 onwards. After these criteria were applied, the abstracts of the documents were screened for relevance, and then subsequently the whole article reviewed with regards to requirements of PV systems. It should be noted that duplicate documents found when conducting the search in PubMed were excluded as they had already been included when conducting the search in Scopus. Furthermore, Google Scholar was consulted for serendipitous findings and relevant articles were included in the study. A total of 15 documents were identified to use as a basis for identifying PV system requirements. The process is summarised in Table I.

TABLE II. INFORMATION ON SYSTEMATIC REVIEW

Search base	Key words or phrases used	Number of documents after applying criteria points	Number of documents after abstract screening	Number of documents after final screening
Scopus	Pharmacovigilance W/5 'requirements OR characteristics'	86	17	7
PubMed	Pharmacovigilance AND requirements	176	14	5
Google Scholar	Pharmacovigilance AND requirements	-	-	3
Total documents examined				15

IV. FINDINGS

In this section the requirements identified from consulting the *pharmaceutical value chain challenges landscape*, Section III, Subsection A and from conducting the systematic literature review, Section III, Subsection B, are given.

A. Collected Data: Requirements identified

After consulting the relevant documents identified in the systematic literature review, Section III, Subsection B, a total of 30 requirements for an effective PV system were identified. Table II provides a summary of these PV requirements. Some of the requirements that were most prominent in the literature were; that PV education should form a more integral part of the healthcare system and that proper communication channels should exist between the different parties involved.

Furthermore, the challenges landscape was also consulted to identify the unique requirements the *pharmaceutical value chain challenges landscape* call for in the niche PV system. Each of the 7 challenges groups, as shown in the challenges landscape in Addendum A, were investigated to identify the unique requirements that challenges group calls for. Once again PV education was one of the most demanding requirements identified as 6 out of the 7 challenges groups call for some form of PV education. Furthermore, there were also unique requirements identified from the challenges landscape such as that quality control checks in the niche PV system should incorporate traditional medicines, sub-standard drugs and counterfeit drugs. All the requirements identified from the challenges landscape are shown in Table III.

B. Analysis of data: Developing core set of requirements

Drawing from the information gained in Section IV, Subsection A, it is clear that there is a broad spectrum of requirements when considering PV systems. Thus, to ensure that the niche PV system considers all the necessary requirements identified from both literature and from the challenges landscape, the requirements discussed above were reviewed and combined to ultimately propose one set of requirements for the niche PV system. However, reviewing the two sets of requirements, Table II and Table III, it was found that certain requirements consider the same concept.

Similar and/or complementary requirements were thus grouped together in order to propose a core set of requirements for the niche PV system; these groups are: reporting system, PV education, quality, communication, stakeholders' roles, consumer involvement, reporting forms, new-released drugs, and databases.

However, to ensure that the requirement specification is relevant to this specific niche environment when considering the context of the challenges landscape, i.e. MPP drug provision systems, the core set of requirements were reviewed to ensure that the proposed final set of requirements accounts for the needs of this specific environment.

The core set of niche PV requirements is provided in the following section.

C. Core set of niche PV requirements

After the screening process was conducted a total of 10 core requirements are identified that the niche PV system will have to satisfy to be able to perform effectively in the MPP drug provision systems. This core set includes requirements such as, having a national PV centre, PV education, quality control systems, clear communication channels, specific ADR reports, and clearly defined stakeholder roles in place for effective drug monitoring. The 10 core requirements are listed in detail below.

1. An effective system for the reporting and managing of ADRs needs to exist with a national PV centre, designated staff and advisory committees and a well-defined structure.
2. PV Education and ADR education must form an integral part of the healthcare system and all stakeholders must be educated on the importance of PV and their specific roles. PV education should include training programmes, PV subjects in the curriculum of healthcare students and workshop sessions. Furthermore, PV education must also address niche environment-specific conditions such as counterfeit drugs, sub-standard drugs, traditional medications and drug-drug interactions.
3. Effective quality control systems need to be in place throughout the entire PV system from ADR reporting to the storage and managing of the data and information. Furthermore, special attention needs to be paid to the quality control monitoring of counterfeit and sub-standard drugs, traditional medicines and consumer-specific drugs such as paediatric drugs.
4. Clear communication channels need to exist between the different stakeholders involved in the PV system. These communication channels should include creating links between quality control labs and PV centres; government and PV centres; and healthcare professionals, pharmaceutical companies and consumers. Furthermore, it is important that during communication with consumers a professional, yet compassionate nature is exercised.

PV SYSTEM REQUIREMENTS DEFINED IN LITERATURE

	Sources found from systematic review																Occurrence
	[21]	[22]	[23]	[24]	[25]	[26]	[27]	[28]	[29]	[30]	[31]	[32]	[33]	[34]	[35]	[18]	
Requirements found from literature	PV Education needs to be incorporated into the health system (training, studies etc.).	X	X		X	X			X		X			X	X		8
	A reporting system with ADR reporting forms needs to exist.	X		X	X	X			X				X	X			7
	Clear lines of communication need to be implemented.	X							X				X	X	X		5
	Forms of public awareness on PV need to be incorporated into the system.			X					X	X				X			4
	PV needs to be introduced in undergraduate and graduate levels of teaching.		X			X			X	X							4
	There must be a clinical trial and post-marketing database for specific drug roll-outs.	X				X	X						X				4
	A national PV centre needs to exist with designated staff and roles and well-defined structure.	X							X					X			3
	The PV plan should take into account risk identification during product development and risk management.	X			X									X			3
	Regular audits and inspections of pharmaceutical companies by healthcare workers need to be implemented.		X	X					X								3
	The roles of the stakeholders need to be clearly defined.		X	X		X											3
	Proper quality management and control systems need to be in place.	X		X					X								3
	All organisations involved with PV need to embrace the concept of quality control and have a collaborative, transparent proactive behaviour.	X		X	X												3
	Qualified personal must be in charge of PV.		X		X				X								3
	Database for the collecting and managing of ADRs needs to exist.	X												X			2
	A PV advisory committee needs to exist and assist on technical matters.	X	X														2
	Additional monitoring is required for new released drugs.	X				X											2
	Knowledge on the safety profile of medicines has to be in place.	X							X								2
	Specific populations/ patients need to be considered when setting up a PV system.	X										X					2
	Reports need to contain all relevant information and if important info is omitted, a system must be in place to contact reporter/healthcare unit to verify the case.					X						X					2
	Special attention needs to be placed on drugs that are suspected for defects.	X														X	2
	Certain drug safety aspects need to be incorporated, such as drug interactions and assessing the contribution of 'inactive' ingredients.	X														X	2
	During drug development, companies need to consider what type of safety information will be required during post-marketing phase, and plan PV activities accordingly.	X					X										2
	In clinical trials, improvements in the mode of safety data collection, timelines, duplication, harmonization, and coverage need to be explored.	X											X				2
	A proactive approach with regards to reporting needs to be taken.				X												1
	ADR reporting must be compulsory to some extent for healthcare professionals.					X											1
	Traditional medicines should be incorporated into national PV programmes.															X	1
	Drug labels must be visible, readable and easy to identify by consumers and healthcare workers especially the section on ADRs.							X									1
	Low-cost reporting solutions at international standards are required.								X								1
	Specific patient and drug information must be present in the ADR reports, such as medical history, age, etc.											X					1
	Generic drugs must be treated as a new released drug and follow all the necessary safety reporting requirements.											X					1
	Improvement in the financial burden by reallocating funds to PV systems.												X				1

PV SYSTEM REQUIREMENTS BASED ON CHALLENGES LANDSCAPE

Requirement Specification For Challenges Landscape				
No	Group	Pharmaceutical Value Chain	Challenges	Requirements
1.	Supply and distribution	Supply, drug development & manufacturing	Specialized drugs, pediatric drugs, traditional medicines	Proper good manufacturing practices (GMP) have to be in place. PV education systems need to incorporate education on specialised drugs and the impacts they have on drug safety. Communication between the drug manufactures (pharmaceutical companies) and the PV stakeholders have to be in place. Quality control over ingredients used in traditional medicines have to be in place. Education needs to incorporate knowledge on drug-drug interactions.
2.		Distribution	Supply, drug shortages, drug stock-outs	Proper good manufacturing practices (GMP) and good distribution practices (GDP) have to be in place. Good quality management systems need to be in place for drug distribution systems. There should be proper funding system in place to improve infrastructures.
3		Product, patient usage	Drug-drug interactions, ADR, drug adherence	Knowledge on how certain drugs interact with other drugs and lead to serious ADRs have to be incorporated. The PV system must be able to locate ADRs in a quick and easy manner and in the case that a dangerous drug is identified it should be removed as soon as possible. Healthcare workers must be able to identify an illness and initiate treatment as soon as possible. Generic drugs need to be seen as new role-out drugs and follow safety reporting requirements. Healthcare workers need to have professional, yet caring nature when working with patients. Patients need to be educated on the process of their treatment, as well as what ADRs are and how they implicate drug adherence.
4		Patient usage	Drug Resistance	Patients need to be educated on the process of their treatment and how ADRs impact drug adherence. Patient drug adherence needs to be improved to ensure that drug resistance does not occur during the treatment process. Proper quality monitoring systems have to be in place to monitor quality of drugs taken by patients and remove all sub-standard drugs and counterfeit drugs.
5	Quality	Supply, drug development & manufacturing	Quality, dosages, labelling	Proper good manufacturing practices (GMP) have to be in place. Proper quality control checks during the labelling process must be incorporated. The inclusion of additional safety information is required for certain drugs on the labels. The label of drug medications must be easily visible, especially the section on ADRs. Patients and health care professionals must easily be able to identify this section. Research and development (R&D) must be improved to include quality checks.
6		Product	Quality, counterfeit, sub-standard drugs	Proper good manufacturing practices (GMP) have to be in place. Generic drugs need to be seen as new role out drugs and follow safety reporting requirements. Quality checks have to be in place to identify fraudulent drug products. Links need to exist between quality control labs and PV centres. Quality control over ingredients used in drug manufacturing have to be in place. PV analysts should have access to the drug manufacturing process (as well as have access to records that are made during manufacturing). Quality monitoring over patients taking drugs have
7	Monitoring	Monitoring	Integrity of the system, record keeping, late initiation, lack of reporting	Healthcare workers need to have professional, yet caring nature when working with patients. ADR reporting must be compulsory to some extent to all healthcare workers. Education on ADRs, and how to properly report ADRs in the healthcare system must be in place. Proper storage of patient healthcare records and reports are needed, includes ADR reports.
8	Culture	Entire PV System	PV culture	PV should involve all the stakeholders throughout the entire process. PV education should be implemented for all students in healthcare and include aspects of the challenges that are faced within unique areas. PV culture should be improved in the healthcare system.
9	Education	Signal detection, evaluation & investigation, taking action	PV education, KAP, training programmes, curriculum	Knowledge, attitude and practices (KAP) of PV must be integrated throughout the whole system and involve all stakeholders. Training programmes on how to report ADRs and monitor ADRs must be implemented in the healthcare system. All stakeholders need to be educated on PV and the importance thereof. The curriculum for students in the healthcare system needs to incorporate the education of PV in some manner such as implementing a subject or training program. Consumers/ patients need to be educated on issues such as drug adherence and drug resistance as well as the reporting of ADRs. The training programmes and other forms of education need to incorporate the challenges identified by inadequate manufacturing. The PV system needs to be able to operate and work effectively without having an extensive amount of resources or funds available. There needs to be a clear line of communication between government and healthcare workers, when it comes to decision making and taking actions. PV education and PV culture must be intergrated within the government or within a sector of the department. Government needs to reprioritising funding and resources towards PV.
10	Stakeholders	Evaluation & investigation, taking action, communication	Government, limited resources, lack of finances	Stakeholders involvement should extend from PV system to manufacturing and distribution of pharmaceutical drugs. All stakeholders need to gain some education and knowledge on PV and the importance thereof. There needs to be a clear line of communication between healthcare workers and the pharmaceutical companies when ADRs are detected. Healthcare workers should be educated on how to professionally and compassionately work with their patients.
11		Entire PV system	Stakeholders, pharmaceutical companies, pharmacists, doctors	For specialised consumers (pediatric/ pregnant) more care should be taken with regards to monitoring of ADRs. Consumers need to be informed and educated on ADRs and the dangers associated with them.
12		Signal detection, evaluation investigation, taking action	Consumers, pediatric/ pregnant, traditional medicines	Education on PV, drug safety monitoring and ADR reporting needs to be implemented and integrated into the healthcare system. Consumer feedback with regards to ADR reporting must be in place. The communication between consumers and the healthcare workers needs to be professional yet compassionate. Guidelines on ADR reports need to be in place. Proper quality control with regards to reporting of ADRs, and the monitoring process must be in place. The reporting forms (or other similar reporting method) must incorporate specific condition/ criteria for the area/ region and drug that is launched. Clear communication channels have to exist between all different stakeholders in the healthcare system.
13	ADR reporting and process	Entire PV system	ADR detection, confidentiality & ethics, under reporting, quality of data, communication	

5. The different stakeholders' roles and responsibilities need to be clearly defined within the PV system. This includes the aspect that pharmaceutical companies need to be more proactively involved with drug safety monitoring; government needs to be actively involved with the implementation of National PV systems; and that healthcare workers need to assist with the identification, monitoring and reporting of ADRs.

6. The PV system needs to encourage patient involvement, by implementing and supporting consumer reporting. Thus, public awareness and consumer feedback sessions need to form an intricate part of the PV system. Furthermore, more care should be taken with specialised consumer groups such as pregnancies/ paediatrics.

7. A niche environment specific ADR report needs to be designed that will not require previously captured information to be included but will still ensure that all

relevant information is obtained. Furthermore, in the case where important information is omitted, a system must be in place to contact reporter/healthcare unit to verify the case.

8. Additional monitoring is required for newly released drugs and generic versions of drugs.

9. There must be a clinical trial and post-marketing database for specific drug roll-outs that can be accessed by PV centres so that previously captured patient information does not have to be captured again.

10. The PV system must be able to work effectively by identifying, reporting and monitoring ADRs without requiring an extensive amount of financial or human resources.

After identifying the ten core requirements it was found that there is not only one area, but a range of different aspects that have to be addressed when developing a niche PV system. These aspects include operational management, quality management, and educational practices. For the niche PV system to function and operate effectively all these different requirements have to be addressed.

V. CONCLUSION AND FURTHER RESEARCH

This article focused on addressing the challenges that arise due to the implementation of the MPP and those existing challenges found in traditional PV systems, by developing a requirement specification for a niche PV system that will address the unique needs called for by MPP drug provision systems.

In this article, a number of approaches were used to ultimately develop a core set of niche PV system requirements. The requirement specification was based on insights gained from consulting literature on PV requirements, advising the *pharmaceutical value chain challenges landscape* and assessing the ability of such a PV system to operate in the environment of the MPP drug provision systems.

However, it should be noted that there are context specific aspects that limit this study. This study investigates the development of a requirement specification for a niche PV system and it was designed for the environment of the MPP drug provision systems. It is thus specifically designed for developing countries that have inadequate drug manufacturing and – distribution systems in RLS. The MPP also only address specific drugs for HIV, TB, and Hepatitis C treatments, which further limit the developed niche PV system.

In conclusion this article reaffirms that there is a need for an innovative, niche PV system that will meet the requirements set out in this article. At this stage it is envisioned that the most ideal solution would be to propose the development and implementation of a mobile application as the niche PV system solution, as this form of ICT would be able to fulfil most of the PV requirements; such as being a less time-consuming, resource-limited solution that can include other operations such as PV education. However, it is also clear that there is a need to look at the entire pharmaceutical value

chain, from R&D phase to drug monitoring phase, from a system perspective to identify other forms of ICT to address the challenges that arise in these MPP drug provision systems.

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ADDENDUM A

		Supply & distribution										Quality				Monitoring			Lack of Education				Stakeholders Involvement								Reporting & Process									
		Specialized drugs	Pediatric drugs	Traditional medicines	Supply	Shortages	Stockouts	Drug-drug interactions	ADRs	Drug resistance	Drug quality	Design	Labeling	Counterfeit drugs	Sub-standard	Integrity of system	Record keeping	Late initiation	Lack of reporting	Education	RAP	Training	Curriculum	Government	Local resources	Lack of funding	Pharmaceutical companies	Doctors	Pharmacists	Consumers	Healthcare providers	Traditional	ADR detection	Confidentiality of data	Under-reporting	Communication	Quality of data			
Supply & distribution	Specialized drugs	X	X								X					X				X													X							
	Pediatric drugs										X										X												X							
	Traditional medicines										X									X													X							
	Supply				X	X			X	X	X			X											X	X	X	X												
	Shortages					X			X	X	X														X	X	X	X												
	Stockouts								X	X	X														X	X	X	X												
	Drug-drug interactions							X																	X	X	X	X												
	ADRs								X	X	X	X	X						X	X		X			X	X	X	X		X	X		X	X						
	Drug resistance									X								X	X		X				X	X								X	X					
	Drug quality										X		X	X	X						X					X	X													
Quality	Quality											X	X	X	X									X	X															
	Design												X												X															
	Labeling													X											X															
	Counterfeit Drugs														X										X															
	Sub-standard															X									X															
Monitoring	Integrity of system																																							
	Record keeping																X								X	X														
	Late initiation																								X	X														
	Lack of reporting																								X	X														
Lack of Education	Education																				X	X																		
	RAP																				X	X	X																	
	Training																				X	X	X																	
	Curriculum																				X	X	X																	
	Government																							X		X														
Stakeholders Involvement	Local resources																								X	X														
	Lack of funding																																							
	Pharmaceutical companies																																							
	Doctors																																							
	Pharmacists																																							
	Consumers																																							
	Healthcare providers																																							
	Traditional																																							
	ADR detection																																							
	Confidentiality of Ethics																																							
Reporting & Process	Under-reporting																																							
	Communication																																							
	Quality of data																																							

Fig. 1. Relationship diagram of challenges landscape

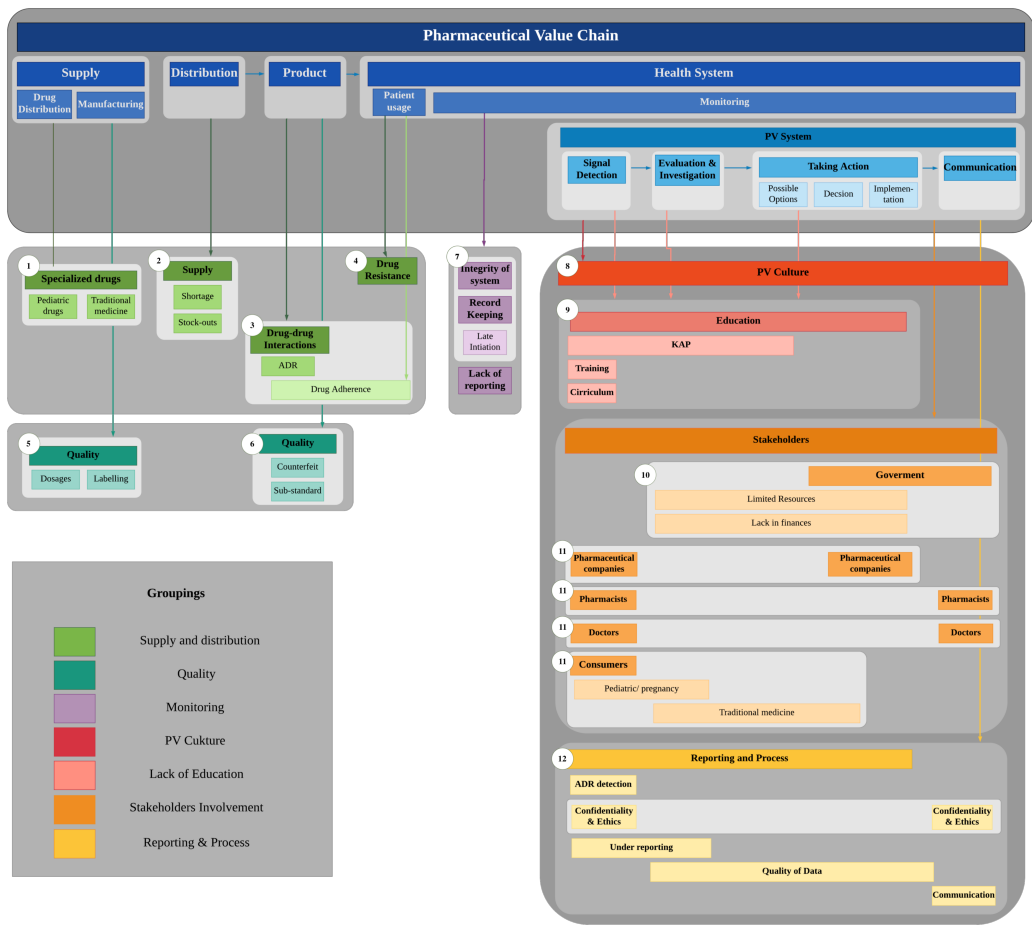


Fig. 2. Schematic representation of challenges landscape

Appendix B. Additional information for PVCCL

In this appendix additional information regarding the systematic literature reviews conducted to develop the PVCCL is found.

The following sections are included:

B1: Challenges related to PV challenges landscape

B2: Challenges related to MPP, RLS and specific illnesses landscape

B.1. PV related Challenges

Table B.1 provides an overview of the occurrence of the different challenges documented in each year.

Table B.1: Overview of occurrences in PV challenges

		Date																Total
		2000	2002	2004	2005	2006	2007	2008	2009	2010	2011	2012	2014	2015	2016	2017	2018	
Occurrence of challenges in systematic review	Stakeholders			2			1			7	1	1	4	5	2	2	3	26
	Education	1		1						4	1	1	1	3	1	1	2	16
	under reporting			2						3	1		2	3	1			12
	KAP						1			4	1			3	1		1	11
	quality of data	1		1				1		1		1	2			2		9
	Training									2	1		1	2	1		2	9
	consumer reporting			1			1						1	2		1	2	8
	pharma companies			1						2	1		2	1		1		8
	ADR reporting/id		1	1		1					1		1			1		6
	limited resources				1	1				1	1		1				1	6
	Doctors									2			1		1		1	5
	Herbal medicine						1							2		1		5
	communication	1								1			1	1				4
	finances					1				1	1			1				4
	government									3							1	4
	Pharmacists									2		1		1				4
	Specific groups						1						1	2				4
	ethical	1								1							1	3
	Insufficient amount of data										1			1		1		3
	standardised reporting								1				1			1		3
	Pregnant women/ped									1	1			1				3
	Data process	1		1														2
	self-medication						1				1							2
	students													1	1			2
	Deduction and monitoring									1								1
	Media			1														1
	off label usage								1									1
	PV culture									1								1

B.2. MPP, disease burden associated with MPP and RLS related challenges

In Table B.2 an overview of the occurrence of the challenges found in literature is provided

Table B.2: Overview of occurrences of challenges related to in MPP, disease burden associated with MPP and RLS

			Date								
			2010	2011	2012	2013	2014	2015	2016	2017	Total
Occurrences of challenges in systematic review	Drug Manufacturing & specific illnesses	Co-infections	1	1	1	1		1			5
		Paediatric drugs	1	1				1	1	1	5
		Dosages		1		1			1		3
		Specialised drugs		1				1	1		3
		Traditional medicine	2							1	3
		Labelling				1				1	2
	Combination of distribution and RLS	Drug supply		2		1	2				5
		Drug stock-outs	1	1		1		1			4
		Drug shortages		1					1		2
	Combination of manufacturing, distribution and RLS and specific illnesses	ADR		2	2	1	3	2	5		15
		Drug adherence	1	2	1	2	3	2	1		12
		Quality	3	1		1	2	2	1	2	12
		Drug-drug interactions				2		3	1		6
		Drug resistance	1	1		2		1	1		6
		Counterfeit drugs			1	1	1			1	4
		Substandard drugs	1			1	1	1			4
	RLS	Record-keeping	2				1	1	1	1	6
		Lack of safety reporting	2	1			1		1		5
		Late ART Initiation	1	2			1				4
		Data					1	1	1		3
		Integrity of system	1				1				2
	RLS & specific illnesses	Diagnostics testing	1					3	1	2	7
		Laboratory	1				1	2		1	4
		Knowledge and awareness			1			1		1	3
		Poor healthcare infrastructure				1		1	1		3

Appendix C. Additional information on Requirement Analysis

This appendix contains information regarding the three systematic literature reviews that were conducted in Chapter 4, with reference to the requirement analysis approach.

The following sections are included:

C1: Requirements related to traditional PV systems

C2: Requirements related to HIV, TB and Hepatitis C

C3: Requirements related to RLS

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C.1. Requirements related to traditional PV systems

Table C.1 provides an overview of the different requirements identified related to PV systems and the occurrence of each of these requirements in the respective document.

Table C.1: Occurrence of requirements related to PV systems

	Requirement group	Specific requirement	Sources found from systematic review															0	
			WHO Min	1	2	3	4	5	6	7	8	9	10	11	12	13	14		15
Requirements found from literature	Education	PV Education needs to be incorporated into the health system (training, studies etc.).		X	X		X		X			X		X			X	X	8
	Effective system	A reporting system with ADR reporting forms need to exist.	X			X	X		X			X				x	X		7
	communication	Clear lines of communication needs to be implemented.	X									X				X	X	X	5
	patient involvement	Some form of public awareness on PV needs to be incorporated into the system.				X						X	X				X		4
	database	There must be a clinical trial and post-marketing database for specific drug roll-outs.		X					X	X					X				4
	Education	PV needs to be introduced in undergraduate and graduate levels of teaching.			X				X			X	X						4
	Quality	Regular audits & inspections of pharmaceutical companies by healthcare workers need to be implemented.			X	X						X							3
	Stakeholders	Stakeholders roles need to be defined clearly.			X	X			X										3
	Effective system	The PV plan should take into account risk identification during product development and risk management.		X			X										X		3
	Quality	Quality management and control systems need to be implemented.		X		X						X							3
	Stakeholders	All organizations involved with PV needs to embrace the concept of quality control and have a collaborative, transparent proactive behaviour.	X		X	X													3
	Education	Qualified personal in charge of PV.			X		X					X							3
	Effective system	A national PV centre needs to exist with designated staff and roles and well defined structure.	X									X					X		3
	Database	Computer systems used for PV should be validated and included the use of safety information outside drug safety functions (call centres).				X	X												2
	Reports	Reports need to contain all relevant information and if important info is omitted, a system must be in place to contact reporter/healthcare unite to verify the case.						X						X					2
Specialised drugs	Special attention needs to be placed on drugs that are suspected for defects.		X														X	2	

	Requirement group	Specific requirement	Sources found from systematic review															Occ.		
			WHO Min	1	2	3	4	5	6	7	8	9	10	11	12	13	14		15	
	specialised drugs	Certain drug safety aspects need to be incorporated such as drug interactions and assessing the contribution of 'inactive' ingredients.		X														X	2	
	Effective system	During drug development companies need to consider what type of safety information will be required during post marketing phase and plan PV activities accordingly.		X							X								2	
	Clinical trials	In clinical trials, improvements in the mode of safety data collection, timelines, duplication, harmonization, and coverage need to be explored.		X													X		2	
	Database	Database for the collecting and managing of ADRs needs to exist.	X															X	2	
	Effective system	A PV advisory committee needs to exist and assist on technical matters.	X	X															2	
	Specialised drugs	Additional monitoring is required for new released drugs.		X						X									2	
	Education	Increase knowledge on the safety profile of medicines.		X									X						2	
	Niche specific	Specific populations/ patients need to be considered when setting up a PV system.		X											X				2	
	Stakeholders	Pharmaceutical companies need to be involved in PV and ADR reporting.				X			X										2	
	Stakeholders	Pharmaceutical companies need to have trained staff.				X								X					2	
	Database	Using literature to identify cases.						X											1	
	Reporting process	A more proactive approach with regards to reporting needs to be taken.						X											1	
	Patient involvement	Pharmaceutical companies should have someone in charge for handling of PV.				X													1	
	Reporting process	ADR reporting must be compulsory for healthcare professionals.								X									1	
	Niche specific	Creating a single country-specific adverse event reporting form to be used by all.								X									1	
	Specialised drugs	Necessary that traditional medicines incorporated into national PV programmes.																	X	1
	Labels	Drug labels must be visible, readable and easy to identify by consumers and health care workers especially the section on ADRs.											X							1
	Reporting process	Low cost reporting solutions at international standards are required.												X						1

	<i>Requirement group</i>	<i>Specific requirement</i>	<i>Sources found from systematic review</i>																	<i>O</i>
			<i>WHO</i>	<i>Min</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>	<i>9</i>	<i>10</i>	<i>11</i>	<i>12</i>	<i>13</i>	<i>14</i>	<i>15</i>	
	Specialised drugs	Generic drugs must be treated as a new released drug and follow all the necessary safety reporting requirements.														X				1
	Finances	Improvement in the financial burden by reallocating funds to PV systems.															X			1

C.2. Requirements related to HIV, TB and Hepatitis C

Table C.2 provides additional information related to the requirements identified associated with the disease burden of HIV, TB and Hepatitis C.

Table C.2: Occurrence of requirements related to HIV, TB and Hepatitis C

	<i>Requirement group</i>	<i>Specific requirement</i>	<i>Sources found from systematic review</i>																			<i>Occurrence</i>
			<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>	<i>9</i>	<i>10</i>	<i>11</i>	<i>12</i>	<i>13</i>	<i>14</i>	<i>15</i>	<i>16</i>	<i>17</i>	<i>18</i>	<i>19</i>	
<i>Requirements found from literature</i>	Education	PV Education should form an integral part of the system. PV education should also be standardised.	X		X				X	X		x			X			X		X		8
	Reporting process	More active monitoring systems are required. Additional or other PV methods/ technique to be incorporated.	X	X				X	X	X							X					6
	Education	PV education should be target at specific groups of people. Patients should be educated on their specific ADRs	X	X								X			X	X						5
	Community	Community involvement should form an integral part of the system.			X				X		X			X								4
	Database	All data collected to be entered into some form of a database	X						X								X			X		4
	Report	Standardised ADR reporting should be used			X												X			X		3
	Niche environment	The system should take the environment into account (for example lack of computers, internet etc.)	X														X	X				3
	Vulnerable patients	Special care should be taken for specific patients such as patients who are on first line regime	X	X												X						3
	Reporting process	ADR reporting should be made compulsory to some extent or healthcare workers should receive rewards for reporting			X	X															X	3
	Education	Improved adherence of illness (HIV treatment) - provide basic education and counselling on treatment				X							X			X						3
	Education	Training regarding countries specific PV guidelines							X	X								X				3
	Quality control	Regular quality control checks to be performed						X	X								X					3
	Communication	Communication & harmonisation between facilities								X		X										2
	Education	Insure there are not incorrect believes - like that TB can be cured using herbal medicines								X		X										2

	<i>Requirement group</i>	<i>Specific requirement</i>	<i>Sources found from systematic review</i>																			<i>Occurrence</i>
			<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>	<i>9</i>	<i>10</i>	<i>11</i>	<i>12</i>	<i>13</i>	<i>14</i>	<i>15</i>	<i>16</i>	<i>17</i>	<i>18</i>	<i>19</i>	
	Stakeholders' roles	Patients should be treated professional but compassionate (not discriminated against patients with certain illness)										X	X									2
	Report	Reports need to be patient and illness (treatment) specific.	X	X																		2
	Database	The specific drugs and treatments need to be listed on PV databases	X						X													2
	Patient involvement	Patient involvement should form part of the system.							X							X						2
	Vulnerable patients	More care should be taken when considering ADR reporting of older patients		X															X			2
	specialised drugs	Special focus should be taken with regards to traditional monitoring					X					X										2
	Stakeholders' roles	Designated person in charge of PV activities								X												1
	Education	PV culture should form an integral part of the system						X														1
	Quality control	The system should focus on reporting quality of drugs to report suspectable counterfeit & sub-standard drugs						X														1
	Vulnerable patients	Monitor patients who are on their first line of treatment (ensure they do not stop the treatment)														X						1
	Report	Terms/ words in reports should be consistent. For example adverse reaction vs adverse event.															X					1
	Report	Ensure viability of ADR reports																X				1
	Public awareness	Targeted interventions should be aimed at colleague students														x						1

C.3. Requirements related to RLS

In this section additional information regarding the requirements identified related to RLS is provided in Table C.3.

Table C.3: Occurrence of requirements related to RLS

	Requirement group	Specific requirement	Sources found from systematic review												Occurrence
			33	37	41	35	40	32	36	6	38	34	39	31	
Requirements found from literature	PV education in academia	PV Education should form an integral part of the system. PV education should also be standardised.	X	X		X		X		X		X		X	7
	Environment specific system	The PV system needs to be region specific and take the specific environments' needs into account		X					X		X		X		4
	Reporting process and reporting forms	Standard procedures	X		X	X					X				4
	PV education in academia	Capacity building should be integrated in the PV system	X						X			X			3
	Environment specific system	Specific populations/ patients need to be considered when setting up a PV system.				X			X				X		3
	Reporting process and reporting forms	The ADR reporting forms should be easy to complete, non-time consuming and resource limited friendly					X			X	X				3
	Additional reporting	More active monitoring systems are required. Additional or other PV methods/ techniques to be incorporated.		X		X									2
	Link to clinical trials	The database for the PV system should be linked to clinical trial databases			X				X						2
	Link to clinical trials	The PV system should be linked to clinical trials and PV training should be introduced during the clinical trial phase.	X						X						2
	Communication & Feedback	Clear lines of communication needs to be implemented.		X						X					2
	Communication & Feedback	Feedback processes need to be incorporated to keep patients informed about the process.								X		X			2
	PV education in academia	PV education should be implemented in the academia. This entails the inclusion of PV subjects into undergraduate programmes.								X					1

	Requirement group	Specific requirement	Sources found from systematic review												Occurrence
			33	37	41	35	40	32	36	6	38	34	39	31	
	Additional reporting	Cohort Event Monitoring (CEM) and Targeted Spontaneous Reporting should be investigated as possible additional methods				X									1
	Communication & Feedback	Communication channels with the MRA (Medicine Regulatory Authorities)				X									1
	Consumer involvement	Consumer in reporting of ADRs is required.								X					1
	Environment specific system	System must be able to identify ARS as soon as possible									X				1
	Reporting process and reporting forms	Innovative ways of capturing data in RLS is required								X					1
	Reporting process and reporting forms	Standard terminology should be used in the reports etc.				X									1
	Reporting process and reporting forms	The reports should be available in the region/ countries' local languages.								X					1
	Remuneration	Reporting should be made compulsory or some form of remuneration should be granted								X					1
	National strategy	The Government should form an integral part of the system and some form of a national strategy should be implemented		X											1

Appendix D. Preliminary requirement specification

This appendix contains the preliminary requirement specification that considers the environment of the MPP drug provision systems and accounts for the requirements the niche factors call.

The following sections are included:

D1: Requirements related to traditional PV systems

D2: Requirements related to MPP

D3: Requirements related to HIV, TB and Hepatitis C

D4: Requirements related to RLS

D.1. Requirements related to traditional PV systems

³⁶Figure D.1 provides an overview of the preliminary requiremnts related to PV systems.

Factor	Code no	Requirements		Challenges							
		Requirement group	Defined	A	B	C	D	E	F	G	H
				Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
PV	PV 1	Pharmacovigilance education should form an integral part of the system	Pharmacovigilance education needs to be incorporated into the health care system. Pharmacovigilance needs to be introduced in undergraduate and graduate levels of teaching. Qualified personal have to be in charge of pharmacovigilance within the different sectors. Knowledge on the safety profile of medicines have to be increased within the healthcare system. Pharmaceutical companies need to have trained staff.	Specialised drugs, paediatrics, traditional medicines, adverse drug reactions, drug adherence	-	Lack of reporting, late initiation, awareness	-	Pharma-covigilance Culture	Lack of KAP (Knowledge, Attitude and Practices), lack of training , insufficient curriculum	Government, pharmacist, doctors, consumers	Adverse drug reactions detection, under reporting, quality of data
	PV 2	Effective system	A reporting system with ADR reporting forms need to exist. The PV plan should take into account risk identification during product development and risk management. A national PV centre needs to exist with designated staff and roles and well defined structure. A PV advisory committee needs to exist and assist on technical matters.	-	-	record keeping, poor healthcare system	laboratory, diagnostics	PV culture	Lack of KAP, lack of training , cirriculum	Doctors, pharmacists, pharmaceutical companies	ADR detection, confidentiality & ethics, communication, quality of data
	PV 3	Quality control	Regular audits & inspections of pharmaceutical companies by healthcare workers need to be implemented. Quality management and control systems need to be implemented.	Specialised drugs, paediatrics, traditional medicines	Counterfeit, sub-standard, labelling	-	-	-	-	Consumers	Quality of data
	PV 4	Communication	Clear lines of communication have to exist between the different stakeholders within the healthcare system.	Specialised drugs, paediatrics, traditional medicines, shortages, stock-outs	counterfeit, substndard	Late initiation	laboratory, diagnostics	-	-	Government, Pharmaceutical companies Pharmacist, Doctors, Consumers	Quality of data, confidence & ethics, communication
	PV 5	Defining stakeholders roles	Stakeholders roles need to be defined clearly. All organizations involved with PV needs to embrace the concept of quality control and have a collaborative, transparent proactive behaviour. Pharmaceutical companies need to be involved in PV and ADR reporting. Pharmaceutical companies need to have trained staff.	Drug-drug interaction, ADR, drug adherence, drug resistance	quality	Integrity of the system, lack of reporting, poor health systems, Awareness	-	PV culture	lack of KAP, lack of training	Government,Doctors, pharmacists, consumers, limited resources, Pharmaceutical companies	Under reporting, quality of data, confidentiality ðics, communication
	PV 6	Public/consumer involvement	Some form of public awareness on PV needs to be incorporated into the system. Patients need to receive feedback after reporting an ADR	Specialised drugs, paediatrics, traditional medicines, ADRs, drug adherence, drug resistance	-	Awareness, lack of reporting	laboratory, diagnostics	PV culture	Lack of KAP, lack of training , cirriculum	consumers, pediatric, traditional limited resources, limited funding	ADR detection, communication, confidentiality & ethics, under reporting
	PV 7	Databases	There must be a clinical trial and post-marketing database for specific drug roll-outs. Computer systems used for PV should be validated and included the use of safety information outside drug safety functions (call centres). Database for the collecting and managing of ADRs needs to exist. Using literature to identify cases.	-	quality	record keeping, poor healthcare system, lack of reporting	-	-	-	Government,Doctors, pharmacists, consumers, limited resources, Pharmaceutical companies	Quality of data, ADR detection, Confidentiality & Ethics, Communication
	PV 8	Niche environment spesific	Specific populations/ patients need to be considered when setting up a PV system. Creating a single country-specific adverse event reporting form to be used by all.	pediatrics	-	awareness, integrity of system	laboratory, diagnostics	-	-	Consumers, pediatric, traditional	confidentiality & ethics, ADR detection
	PV 9	ADR reports	Reports need to contain all relevant information and if important info is omitted, a system must be in place to contact reporter/healthcare unite to verify the case.	Specialised drugs, paediatrics, traditional medicines, ADRs, drug adherence, drug resistance	quality, sub-standard, counterfeit	Awareness, lack of reporting, poor health systems, late initiation	-	-	-	Consumers, pediatric, traditional, doctor, pharmacists	ADR detection, communication, quality of data
	PV 10	Special drugs	Special attention needs to be placed on drugs that are suspected for defects. Certain drug safety aspects need to be incorporated such as drug interactions and assessing the contribution of 'inactive' ingredients. Additional monitoring is required for new released drugs. Necessary that traditional medicines incorporated into national PV programmes. Generic drugs must be treated as a new released drug and follow all the necessary safety reporting requirements.	Specialised drugs, paediatrics, traditional medicines, drug-drug interactions, ADRs	quality, sub-standard, counterfeit	Late initiation, record keeping	laboratory, diagnostics	-	-	consumers, pediatric, traditional	quality of data
	PV 11	Reporting process	A more proactive approach with regards to reporting needs to be taken. Low cost reporting solutions at international standards are required. ADR reporting must be compulsory for healthcare professionals.	ADR, drug adhereece	-	Late initiation, lack of reporting, awareness, poor healthcare system	-	PV culture	-	Doctors, pharmacists, consumers, pharmaceutical companies, limited resources, lack of finances	Under reporting, ADR detection
	PV 12	Link to clinical trials	In clinical trials, improvements in the mode of safety data collection, timelines, duplication, harmonization, and coverage need to be explored.	-	-	record keeping, lack of reporting	-	-	-	limited resources	communication
	PV 13	Drug labels	Drug labels must be visible, readable and easy to identify by consumers and health care workers especially the section on ADRs.	-	Quality, labelling	-	-	-	-	Doctors,	-

Figure D.1: Preliminary requirement specification related to PV systems

³⁶ These challenges refer to all the challenges identified through systematic literature reviews that the factors (MPP, specific illnesses, RLS and traditional PV systems) attribute to and that the niche PV system needs to address. A total of 8 challenges groups were identified, listed A-H and a total of 43 challenges were identified. A shorted list is provided below.

A – **Supply & distribution:** Specialized drugs, paediatric drugs, traditional medicines, supply, shortages, stock-outs, drug-drug interactions (*as a change in the effect of the drug when it is taken together with another drug and it can often lead to ADR*), adverse drug reactions (*any response to a drug which is noxious and unintended*), drug adherence (*the act where patients abide to the recommendations made regarding the dosage, timing and frequency of medication taken*), drug resistance (*the response to a drug in a susceptible parasite population decreases significantly*)

B – **Quality:** Quality, dosages, labelling, counterfeit drugs (*medical products that deliberately/fraudulently misrepresent their identity, composition or source*), sub-standard drugs (*authorized medical products that fail to meet either their quality standards or specifications, or both*)

C – **Monitoring:** Integrity of the system (*the support, integrity and confidentiality of the health care workers has seen to have an impact on treatment*), record keeping, late initiation, lack of reporting, poor health system, awareness (*lack of awareness and knowledge regarding the illness and treatment procedures*)

D – **Testing:** Laboratory (*the poor and limited amount if laboratories and testing infrastructures*), diagnostics (*diagnostic testing is required to predict the correct treatment procedure*)

E – **PV Culture**

F – **Lack of education:** KAP (*knowledge, attitude and Practices associated with PV*), training (*lack of effective PV training programs for healthcare professions*), curriculum (*incorporate PV subjects into the curriculum of healthcare students*)

G – **Stakeholder involvement:** Government, lack of resources (*people, time and money*) lack of finances, pharmaceutical companies, pharmacists, doctors, consumers, paediatric/pregnant, traditional medicine users

H – **Reporting & process:** Adverse drug reaction detection (*identification of ADRs together with the detection of the connection between the ADRs and the drug exposure*), confidentiality & ethics (*trusting the healthcare workers*), under reporting of ADRs, quality of data (*the data gathered from reporting should be of a high quality*), communication (*communication platforms between the different stakeholders have to exist*)

D.2. Requirements related to MPP

Figure D.2 provides an overview of the MPP related requirements from the preliminary requirement specification.

Factor	Code No	Requirements	Challenges							
			Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
MPP	MPP 1	PV Education <i>PV Education should include education on specialised drugs (such as traditional medicines).</i> <i>PV Education should include education on drug-drug interactions</i> <i>Drug manufacturing companies should be informed and educated on the importance of PV</i> <i>Patients need to be educated on what ADRs are and how to report ADRs.</i>	Specialised drugs, pediatrics, traditional medicines, ADRs, drug adherence	-	Lack of reporting, late initiation, Awareness	-	PV Culture	Lack of KAP, lack of training, curriculum	Government, Pharmacist, Doctors, Consumers	ADR detection, Under reporting, Quality of data
	MPP 2	Communication <i>Communication channels between quality control labs and PV centres</i> <i>Communication channels between drug manufacturers and PV centres</i>	Specialised drugs, pediatrics, traditional medicines, shortages, stock-outs	counterfeit, sub-standard	Late initiation	laboratory, diagnostics	-	-	Government, Pharmaceutical companies, Pharmacist, Doctors, Consumers	Quality of data, confidence & ethics
	MPP 3	Funding and finances <i>Proper funding systems should be in place to improve infrastructures and drug monitoring systems.</i>	Supply, shortages, stock-outs	-	Record keeping, late initiation, poor healthcare system	-	-	Lack of KAP, lack of training, curriculum	Limited resources, lack of funding	-
	MPP 4	Reporting process <i>ADR reporting should be made compulsory to some extent for all health care workers</i> <i>The system must ensure the effective capturing and storage of the ADR reports</i> <i>A drug monitoring system must be able to locate ADRs in a quick, easy manner.</i>	-	-	Late initiation, record keeping, lack of reporting, awareness, poor healthcare system	laboratory, diagnostics	PV culture	-	Doctors, pharmacists, consumers, limited resources, lack of funding	Under reporting, ADR detection, confidentiality & ethics, communication
	MPP 5	Stakeholder's roles <i>Healthcare workers must be able to identify an illness and or ADRs and report them as soon as possible.</i> <i>Pharmaceutical companies need to play a vital role in the system.</i> <i>Healthcare workers need to have professional, yet caring nature when working with patients.</i>	Drug-drug interaction, ADR, drug adherence, drug resistance	-	Integrity of the system, lack of reporting, poor health systems	-	PV culture	-	Doctors, limited resources, pharmaceutical companies, pharmacists,	Under reporting, quality of data
	MPP 6	Quality control <i>Special attention needs to be paid to quality control monitoring of counterfeit and sub-standard drugs.</i> <i>Special attention needs to be paid to quality control monitoring of specialised drugs such as traditional medicine and pediatric drugs.</i> <i>Proper quality control checks during the labelling process must be incorporated.</i> <i>Quality monitoring over patients taking drugs have to exist</i> <i>Proper quality control over ingredients used in traditional medicines.</i> <i>Proper good manufacturing practices (GMP) and good distribution practices (GDP) have to be in place</i>	Specialised drugs, pediatrics, traditional medicines, supply, shortages, stock-outs	Quality, counterfeit, sub-standard, dosages, labelling	-	-	-	-	Consumers	Quality of data
	MPP 7	Drug labels <i>The label of drug medications must be easily visible, especially the section on ADRs.</i> <i>Patients and health care professionals must easily be able to identify this section.</i>	-	Quality, labelling	-	-	-	-	Doctors,	-
	MPP 8	Niche environment specific <i>Specific populations/ patients need to be considered when setting up a PV system.</i> <i>The system should be designed specifically for pediatric and traditional medicine users</i> <i>Generic drugs must be treated as a new released drug and follow all the necessary safety reporting requirements.</i> <i>The system needs to take the environments' unique challenges into account such as shortage and stock-outs.</i>	pediatrics	Quality, sub-standard, counterfeit	awareness, integrity of system	laboratory, diagnostics	-	-	Consumers, pediatric, traditional	confidentiality & ethics, ADR detection

Figure D.2: Preliminary requirement specification related to PV systems

D.3. Requirements related to HIV, TB and Hepatitis C

Refer to figure D.3 for an overview of the requirements related to HIV, TB and Hepatitis C.

Factor	Code no	Requirements		Challenges							
		Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
Spec illness	SI 1	Education	PV Education should form an integral part of the system. PV education should also be standardised. PV Education should be target at specific groups of people. Patients should be educated on their specific ADRs Improved adherence of illness (HIV treatment) - provide basic education and counselling on treatment Training regarding countries specific PV guidelines Ensure there are not incorrect beliefs - like that TB can be cured using herbal medicines PV culture should form an integral part of the system	Specialised drugs, pediatric, traditional medicines, supply, Drug adherence, drug resistance	quality, counterfeit, sub-standard	late initiation, lack of reporting, poor healthcare systems, awareness	-	PV culture	Lack of KAP, lack of training, curriculum	Government, Doctors, pharmacists, consumers, pharmaceutical companies	ADR detection, under reporting, quality of data
	SI 2	Reporting process	More active monitoring systems are required. Additional or other PV methods/ techniques to be incorporated.	ADR, drug adherence, drug resistance	-	-	-	PV culture	-	doctors, pharmacists	ADR detection, under reporting,
	SI 3	Reports	Reports need to be patient and illness (treatment) specific. Standardised ADR reporting should be used Terms/ words in reports should be consistent. For example adverse reaction vs adverse event. Ensure availability of ADR reports	Specialised drugs, pediatric, traditional medicines, supply shortages, drug-drug interactions,	quality, counterfeit, sub-standard	late initiation	-	-	-	doctors, pharmacists, pharmaceutical companies	ADR detection, quality of data, confidentiality & ethics
	SI 4	Work organisational factors	The system should take the environment into account (for example lack of computers, internet ect) Reports need to be patient and illness (treatment) specific.	Specialised drugs, pediatric, traditional medicines, supply, Drug adherence, drug resistance	quality, counterfeit, sub-standard	awareness	laboratory, diagnostics	-	-	consumers, pediatric, traditional medicines	under reporting, ADR detection, communication
	SI 5	Vulnerable patients	Special care should be taken for specific patients such as patients who are on first line regime More care should be taken when considering ADR reporting of older patients Monitor patients who are on their first line of treatment (ensure they do not stop the treatment)	drug-drug interactions, ADR drug adherence, drug resistance	-	poor health systems, awareness	-	-	-	consumers	communication, ADR detection,
	SI 6	stakeholders	ADR reporting should be made compulsory to some extent or healthcare workers should receive rewards for reporting Patients should be treated professional but compassionate (not discriminated against patients with certain illness) Designated person in charge of PV activities	-	-	lack of reporting, poor health system, awareness	-	PV culture	KAP, training	Government, Doctors, pharmacists, pharmaceutical companies	communication, under reporting
	SI 7	special drugs	The specific drugs and treatments need to be listed on PV databases Special focus should be taken with regards to traditional monitoring	Specialised drugs, pediatric, traditional medicines, drug-drug interactions	-	awareness	laboratory, diagnostics	-	-	pharmaceutical companies, consumers, pediatric, traditional medicines	ADR detection, quality of data
	SI 8	Quality control	Regular quality control checks to be performed The system should focus on reporting quality of drugs to report susceptible counterfeit & sub-standard drugs	-	quality, counterfeit, sub-standard, dosages, labelling	-	laboratory, diagnostics	PV culture	-	pharmaceutical companies	Quality of data, confidentiality & ethics
	SI 9	Public awareness	Targeted interventions should be aimed at colleague students Patient involvement should form part of the system. Community involvement should form an integral part of the system.	drug-drug interactions, drug adherence, drug resistance	-	late initiation, awareness	-	PV culture	-	consumers, pediatric, traditional medicines	under reporting, ADR detection, communication, confidentiality & ethics

Figure D.3: Preliminary requirement specification related to HIV, TB and Hepatitis C

D.4. Requirements related to RLS

Preliminary requirements related to RLS can be found in Figure D.4.

Factor	Code no	Requirements		Challenges							
		Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
RLS	RLS 1	Education	Pharmacovigilance education should form an integral part of the system. Pharmacovigilance education should also be standardised. Pharmacovigilance education should be implemented in the academia. This entails the inclusion of pharmacovigilance subjects into undergraduate programmes. Capacity building should be integrated in the pharmacovigilance system.	-	-	Late initiation, lack of reporting	-	Pharmaceutical Culture	Lack of KAP (Knowledge, Attitude and Practices), insufficient curriculum	Doctors, pharmacists	Adverse drug reaction detection, under reporting, quality of data
	RLS 2	Additional reporting	Cohort Event Monitoring (CEM) and targeted spontaneous reporting should be investigated as possible additional methods More active monitoring systems are required. Additional or other PV methods/ techniques to be incorporated.	Adverse drug reactions, drug adherence, drug resistance	-	-	-	-	-	Doctors, pharmacists, pharmaceutical companies	Adverse drug reaction detection
	RLS 3	Link to clinical trials	The database for the pharmacovigilance system should be linked to clinical trial databases The pharmacovigilance system should be linked to clinical trials and pharmacovigilance training should be introduced during the clinical trial phase.	-	Quality	Record keeping, poor health system	Laboratory & diagnostics	-	Training	Doctors, pharmacists	Quality of data
	RLS 4	Communication	Clear lines of communication needs to be implemented. Communication channels with the MRA (Medicine Regulatory Authorities) Feedback processes need to be incorporated to keep patients informed about the process.	Supply, shortages, stock-outs	-	Integrity of the system, lack of reporting, poor health system	Laboratory & diagnostics	-	-	Government, limited resources, doctors, pharmacists, consumers, pharmaceutical companies	Communication, under reporting
	RLS 5	Patient involvement	Consumer involvement for reporting	Drug adherence	-	Lack of reporting	-	Pharmaceutical Culture	Lack of KAP (Knowledge, Attitude and Practices), insufficient curriculum	Consumers, doctors, pharmacists, limited resources	Communication, confidentiality & ethics, under reporting, adverse drug reaction detection
	RLS 6	Environment specific system	System must be able to identify adverse drug reactions as soon as possible. The system needs to be region specific and take the specific environments' needs into account. Specific populations/ patients need to be considered when setting up a pharmacovigilance system.	Specialised drugs, supply, drug-drug interactions, adverse drug reaction	-	Awareness	-	Pharmaceutical Culture	-	Consumers, doctors, pharmacists, limited resources	Quality of data
	RLS 7	Reporting process and reporting forms	The process needs to be standardised. Innovative ways of capturing data in resource limited settings are required Standard terminology should be used in the reports. The reports should be available in the region/ countries' local languages. The adverse drug reaction reporting forms should be easy to complete, non-time consuming and resource limited friendly.	Specialised drugs, drug-drug interactions, adverse drug reactions	-	Record keeping, lack of reporting, poor health system	-	-	-	Doctors, pharmacists, pharmaceutical companies, limited resources	Adverse drug reaction detection, under reporting, quality of data
	RLS 8	Remuneration	Reporting should be made compulsory or some form of remuneration should be granted to healthcare workers when they report adverse drug reactions	-	-	Poor health system, lack of reporting	-	Pharmaceutical Culture	-	Doctors, pharmacists, pharmaceutical companies, limited resources	Adverse drug reaction detection, under reporting
	RLS 9	National strategy	The Government should play an integral part of the pharmacovigilance system and some form of a national strategy should be implemented	Supply, shortages, stock-outs	Quality	Poor health system, lack of reporting, integrity of the system	-	Pharmaceutical Culture	Lack of KAP (Knowledge, Attitude and Practices)	Government	Adverse drug reactions detection, communication, under reporting

Figure D.4: Preliminary requirement specification related to RLS

Appendix E. Requirement specification verification information

In this appendix additional information regarding the validation process of the vigilance system requirement specification is provided. This information includes the pre-read documents and questionnaires used during the validation.

The following sections are included:

E1: PV requirement validation documents

E2: MPP requirement validation documents

E3: RLS requirement validation documents

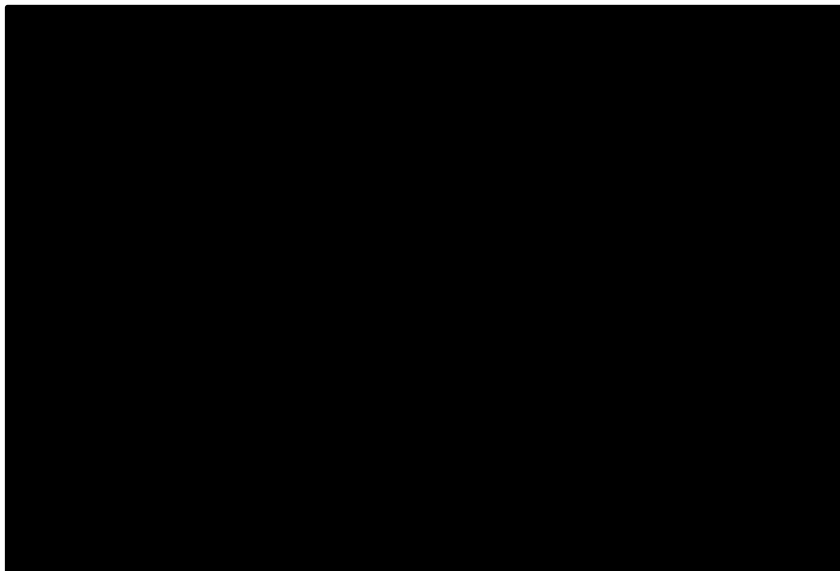
E4: Specific illnesses requirement validation documents

E.1. PV requirement validation documents

Innovative PV: Towards a niche PV system

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1. Introduction

In the modern-day health landscape, there has been a significant change within the pharmaceutical industry with regards to innovative drug manufacturing and distribution systems which calls for improved surveillance and monitoring systems that can support such systems. One such an innovation is the Medicine Patent Pool (MPP)¹ which aims to improve access to affordable drugs for TB, HIV and Hepatitis C in low- and middle-income countries [1].

However it is often the case that these provision systems are deployed in areas that do not have effective 'PV systems'² for the reporting of adverse drug reactions (ADRs) and face the challenge of being implemented in resource limited settings (RLS) [2]. The fact that numerous manufacturers could be utilised through the MPP to generate drugs, intensifies the need to monitor drug quality and once again highlights the need for effective drug safety monitoring and PV systems within this context.

All these factors reaffirm the need for more innovative PV systems to be implemented that will address these niche specific factors. Thus, the aim of this research investigation is to propose a 'niche PV system', through the development of a conceptual framework, that will support the effective and efficient reporting of ADR's for pilot drug roll-out projects in RLS.

¹ The MPP is a public health organisation that was launched in 2010 by UNITAID and aims to improve accessibility and development of life-saving drugs for HIV, TB, and hepatitis C in developing countries through the sharing of technologies and patents [1]. The MPP collaborates closely with industry stakeholders and patent holders to develop licence agreements which allow pharmaceutical companies to manufacture generic versions of drugs, as well as with the World Health Organisation to prioritise these drugs for licensing [21]. Through this innovative drugs are made available to a broader population at a faster rate [21]. In addition to having drugs provided to a broader population through the implementation of the MPP, there are additional advantages such as encouraging research and development and facilitating competition [3], [22], [23].

²The World Health Organisation defines pharmacovigilance (PV) as, "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem"[24]. The key objective of an effective PV system is to report and monitor adverse drug reactions (ADRs) in an attempt to minimise risks [25]. In addition, the identifying and evaluating of previously un- or underreported ADRs is also a vital part of such a PV system. According to the WHO for a PV system to work effectively, data collection from health practitioners, systematic monitoring and analysis of input data is required especially in the case of new drugs that are rolled out [26]. There are still however many challenges to be faced with regards to drug monitoring especially in developing countries [26].

It was decided that a system engineering approach would be used to develop the conceptual framework of the niche PV system, as this approach transforms an operational need into a system solution by breaking down the need into smaller comprehensible parts to address [3]. Refer to figure 1 for a representation of the approach. In conducting this approach the first step was to identify the different factors that would impact the niche PV system. The four factors identified were the MPP, the specific illnesses the MPP address (HIV, TB and Hepatitis C), RLS, and traditional PV systems. Furthermore, to gain a better understanding of these factors, the challenges these factors face when considering drug monitoring (PV systems) were identified through conducting in-depth systematic literature reviews. A brief description of these challenges are provided in Table 1. The next step was to conduct a requirement analysis to identify what unique requirements each of the factors would call for in the niche PV system. The final step of the process would be to conduct a functional analysis that would entail identifying possible solutions to address the requirements of each factor.

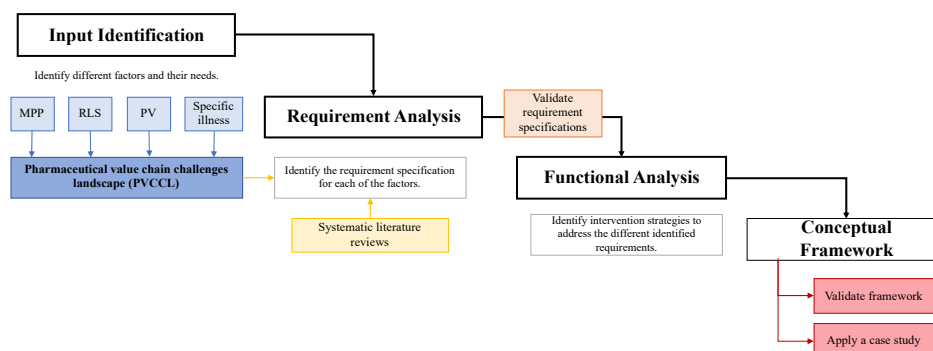


Figure 1: Research methodology

Table 1: Overview of challenges identified

Challenges Group	Challenges identified
Supply & distribution	Specialized drugs, pediatric drugs, traditional medicines, supply, shortages, stock-outs, drug-drug interactions (a change in the effect of the drug when it is taken together with another drug and it can often lead to ADR), adverse drug reactions (any response to a drug which is noxious and unintended), drug adherence (the act where patients abide to the recommendations made regarding the dosage, timing and frequency of medication taken), drug resistance (the response to a drug in a susceptible parasite population decreases significantly)
Quality	Quality, dosages, labelling, counterfeit drugs (medical products that deliberately/fraudulently misrepresent their identity, composition or source), sub-standard drugs (authorized medical products that fail to meet either their quality standards or specifications, or both)

Monitoring	Integrity of the system (<i>the support, integrity and confidentiality of the health care workers has seen to have an impact on treatment</i>), record keeping, late initiation, lack of reporting, poor health system, awareness (<i>lack of awareness and knowledge regarding the illness and treatment procedures</i>)
Testing	Laboratory (<i>the poor and limited amount of laboratories and testing infrastructures</i>), diagnostics (<i>diagnostic</i>)
PV Culture	-
Lack of education	KAP (<i>knowledge, attitude and Practices associated with PV</i>), training (<i>lack of effective PV training programs for healthcare professions</i>), curriculum (<i>incorporate PV subjects into the curriculum of healthcare students</i>)
Stakeholder involvement	Government, lack of resources (<i>people, time and money</i>) lack of finances, pharmaceutical companies, pharmacists, doctors, consumers, pediatric/pregnant, traditional medicine users
Reporting & process	Adverse drug reaction detection (<i>identification of ADRs together with the detection of the connection between the ADRs and the drug exposure</i>), confidentiality & ethics (<i>trusting the healthcare workers</i>), under reporting of ADRs, quality of data (<i>the data gathered from reporting should be of a high quality</i>), communication (<i>communication platforms between the different stakeholders have to exist</i>)

However the purpose of this validation is to address and reaffirm the validity of the requirements identified, focusing specifically on the requirements that a PV system calls for.

2. Requirement specification related to PV

A total of 13 unique requirements were identified related to PV systems, refer to Appendix A.

An individual description of each of the 13 requirements listed PV 1 – PV 13, are given in this section.

PV 1. Pharmacovigilance education needs to form an integral part of the system.

Code no	Requirements		Challenges							
	Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
PV 1	Pharmacovigilance education should form an integral part of the system	Pharmacovigilance education needs to be incorporated into the health care system. Pharmacovigilance needs to be introduced in undergraduate and graduate levels of teaching. Qualified personnel have to be in charge of pharmacovigilance within the different sectors. Knowledge on the safety profile of medicines have to be increased within the healthcare system. Pharmaceutical companies need to have trained staff.	Specialised drugs, paediatrics, traditional medicines, adverse drug reactions, drug adherence	-	Lack of reporting, late initiation, awareness	-	Pharmacovigilance Culture	Lack of KAP (Knowledge, Attitude and Practices), lack of training, insufficient curriculum	Government, pharmacist, doctors, consumers	Adverse drug reactions detection, under reporting, quality of data

One of the most identified needs and requirements when looking at developing a pharmacovigilance system is the aspect of PV education. Literature calls for PV education to form a more vital part within the whole health system [4]–[11]. In a study done by the WHO and the Upsala Monitoring Centre the importance of having drug safety and PV integrated in the medical health curricula is highlighted as well as the lack of research and postgraduate training in this field. The research argues that if healthcare practitioners are confident in their ability to correctly diagnose, manage and prevent ADRs, they would be more likely to report ADRs. Furthermore, when looking at PV education all stakeholders should be actively involved, however the national PV centres and other similar establishments should be seen as the primary teaching bases. Furthermore, PV education should not just be limited to training sessions but should include a variety of different methods, such as conferences, educational programmes and scientific publications [11].

Thus, when looking at the establishing of a PV system proper PV education is one of the main requirements for the system to work and function effectively.

PV 2. Clear lines of communication have to exist within the system.

Code no	Requirements		Challenges							
	Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
PV 2	Communication	Clear lines of communication have to exist between the different stakeholders within the healthcare system.	Specialised drugs, pediatrics, traditional medicines, shortages, stock-outs	counterfeit drugs, substandard drugs	Late initiation	Laboratory, diagnostics	-	-	Government, pharmaceutical companies, pharmacist, doctors, consumers	Quality of data, confidence & ethics, communication

For a system to work and function effectively clear lines of communications between different stakeholders are vital. Thus, for the niche PV system to operate effectively clear channels of communication need to be formed between quality control labs and PV centres; government and PV centres; healthcare professionals and consumers and pharmaceutical companies [8], [10], [11]. Communication and collaboration is also one of the minimum requirements the WHO states a PV system requires

PV 3. The system requires public/consumer involvement.

Code no	Requirements		Challenges							
	Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
PV 3	Public/consumer involvement	Some form of public awareness on pharmacovigilance needs to be incorporated into the healthcare system.	Specialised drugs, paediatrics, traditional medicines, adverse drug reactions, drug adherence, drug resistance	-	Awareness, lack of reporting	Laboratory, diagnostics	Pharmacovigilance Culture	Lack of KAP (Knowledge, Attitude and Practices), lack of training, insufficient curriculum	consumers, paediatric, traditional medicine users, limited resources, limited funding	Adverse drug reaction detection, communication, confidentiality & ethics, under reporting
		Patients need to receive feedback after reporting an ADR								

The proposed niche PV system will require consumer involvement to play a more vital part of the system. This entails involving the consumers more directly with the PV system and improving public awareness with regards to ADR reporting and PV systems [12]. The aspect of including consumer feedback sessions should also be taken into consideration [10].

PV 4. The system requires an effective database for the collecting and managing of reports.

Code no	Requirements		Challenges							
	Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
PV 4	Databases	There must be a clinical trial and post-marketing database for specific drug roll-outs.	-	Quality	Record keeping, poor healthcare system, lack of reporting	-	-	-	Government, doctors, pharmacists, consumers, limited resources, pharmaceutical companies	Quality of data, adverse drug reaction detection, confidentiality & ethics, communication
		Computer systems used for PV should be validated and included the use of safety information outside drug safety functions (call centres).								
		Database for the collecting and managing of adverse drug reactions needs to exist. Literature should be considered to identify safety cases.								

The WHO states that one of the minimum requirements needed for a PV system is that a database for the collecting and the managing of ADRs needs to exist {min requirements}. Although the success of a PV system requires the reporting of ADRs, the managing of the data gathered and the databases that contain the data plays a vital role in the effectiveness of the PV system. The National PV centre is the stakeholder responsible for the managing of the data bases, the collecting of the reports, evaluating of the reports, the identifying of suspicious reactions, and the recommendation of regulatory actions that should be taken [10]. Furthermore, with the growing use of technology in the health system the databases and process of identifying ADRs are more computerised which call for more effective quality control and validation systems to be in place [6], [12].

Thus, the niche PV system will also require the existence of an effective database that will assist the National PV Centres with the managing of the data in the specific environments that face challenges such as limited human resources and lack of funding.

PV 5. A pharmacovigilance centre or reporting system needs to exist.

Code no	Requirements		Challenges							
	Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
PV 5	An PV centre or reporting system needs to exist	<p>A reporting system with adverse drug reaction reporting forms need to exist.</p> <p>The pharmacovigilance plan should take into account risk identification during product development and risk management.</p> <p>A national pharmacovigilance centre needs to exist with designated staff, roles and well defined structure.</p> <p>A pharmacovigilance advisory committee needs to exist and assist on technical matters.</p>	-	-	Record keeping, poor healthcare system	Laboratory, diagnostics	Pharmacovigilance Culture	Lack of KAP (Knowledge, Attitude and Practices), lack of training, insufficient curriculum	Doctors, pharmacists, pharmaceutical companies	ADR detection, confidentiality & ethics, communication, quality of data

Having a well-structured PV system that entails all aspects from collecting and managing ADR reports, clinically evaluating the ADR reports, distinguish ADRs from “noise”, taking regulatory action, and alerting prescribers, manufacturers and the public [7], [8], [10], [12]. Furthermore, the system needs to have designated staff with qualified people in charge as well as an advisory committee to assist with technical matters [4], [8], [10]. Literature has also shown that the PV system should also be integrated in the product development phase with regards to risk identification [6].

PV 6. The system requires effective quality management and quality control systems.

Code no	Requirements		Challenges							
	Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
PV 6	Quality control	<p>Regular audits & inspections of pharmaceutical companies by healthcare workers need to be implemented.</p> <p>Quality management and control systems need to be implemented.</p>	Specialised drugs, pediatrics, traditional medicines	Counterfeit drugs, sub-standard drugs, labelling	-	-	-	-	Consumers	Quality of data

Quality management and control systems need to be integrated within in different sectors and areas of the PV system. Good Pharmacovigilance Practices state that this entails that quality management systems should include clear policies, standard operating procedures, working instructions and job descriptions with regards to drug safety [12]. Furthermore, quality management also entails ensuring that the system is regular reviewed and audited, and that the computers (or other equipment used) are validated and have change control processes in place [12]. All organizations involved with PV needs to embrace the concept of quality control and have a collaborative, transparent proactive behaviour to implementing quality control [4], [8], [12]. Thus for the niche PV system to function effectively it is required that there are effective

quality control systems in place with regular audits and inspections and the different stakeholders involved are all actively involved to ensure quality control is incorporated.

PV 7. St The stakeholders' roles need to be clearly defined.

Code no	Requirements		Challenges							
	Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
PV 7	Stakeholders' roles should be clearly defined	All organizations involved with PV needs to embrace the concept of quality control and have a collaborative, transparent proactive behaviour. Pharmaceutical companies need to be involved in adverse drug reaction reporting. Pharmaceutical companies need to have trained staff.	Drug-drug interaction, adverse drug reactions, drug adherence, drug resistance	Quality	Integrity of the system, lack of reporting, poor health systems, awareness	-	Pharmacovigilance Culture	Lack of KAP (Knowledge, Attitude and Practices), lack of training	Government, doctors, pharmacists, consumers, limited resources, pharmaceutical companies	Under reporting, quality of data, confidentiality & ethics, communication

For the niche PV system to work effectively it is required that all the different stakeholders' (Government, national PV Centres, healthcare practitioner pharmaceutical companies' and customers) roles and responsibilities are clearly defined [4], [6], [7]. It has been seen in literature that pharmaceutical companies need to be more actively involved with the PV process and reporting of ADRs [4], [13], [14]. Furthermore, as stated in stakeholders need to embrace the concept of quality control and training in the PV system In defining the stakeholders' roles it is also necessary to take the specific environment into account for the niche PV system.

PV 8. ADR reporting forms need to contain all relevant information.

Code no	Requirements		Challenges							
	Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
PV 8	Adverse drug reaction reports	Reports need to contain all relevant information and if important information is omitted, a system must be in place to contact the reporter/healthcare unite to verify the case.	Specialised drugs, pediatrics, traditional medicines, adverse drug reactions, drug adherence, drug resistance	Quality, sub-standard, counterfeit	Awareness, lack of reporting, poor health systems, late initiation	-	-	-	Consumers, pediatric, traditional medicine users, doctor, pharmacists	Adverse drug reaction detection, communication, quality of data

For a PV system to operate successfully and effectively it is vital that ADRs are reported, and thus the ADR reporting forms are a vital part of the system [10]. The ADR reporting forms need to contain all the relevant information and some form of standardisation is required for the system to function more effectively. Furthermore, in the case that relevant information is omitted or questioned, the system must be able to verify the report through contacting the necessary parties [9], [13], [15].

PV 9. More care needs to be taken with special drugs.

Code no	Requirements		Challenges							
	Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
PV 9	More care for specialised drugs	<p>Special attention needs to be placed on drugs that are suspected for defects.</p> <p>Certain drug safety aspects need to be incorporated such as drug interactions and assessing the contribution of 'inactive' ingredients.</p> <p>Additional monitoring is required for new released drugs.</p> <p>Necessary that traditional medicines incorporated into national pharmacovigilance programmes.</p> <p>Generic drugs must be treated as a new released drug and follow all the necessary safety reporting requirements.</p>	Specialised drugs, pediatrics, traditional medicines, drug-drug interactions, adverse drug reactions	quality, sub-standard, counterfeit	Late initiation, record keeping	laboratory, diagnostics	-	-	Consumers, pediatric, traditional medicine users	Quality of data

In the case for the niche PV system their requirements that have to be taken into account when looking at the environments where the system will be used, low- and middle-income countries. One such a requirement is to pay more attention to specialised drugs such as traditional medicines which are more prone to be used in these areas. The reactions that inactive ingredients, used in traditional medicines, can cause should be taken into account when developing the niche PV system [4], [11]. Furthermore, this also entails paying more attention to drugs that are suspect of defects as low and middle income countries do have more cases of counterfeit and sub-standard drugs [4], [11].

PV 10. A link needs to exist between pharmacovigilance systems and clinical trials.

Code no	Requirements		Challenges							
	Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
PV 10	Link to clinical trials	In clinical trials, improvements in the mode of safety data collection, timelines, duplication, harmonization, and coverage need to be explored.	-	-	Record keeping, lack of reporting	-	-	-	Limited resources	Communication

The WHO defines clinical trials as any research study that evaluates the health effects by prospectively assigning humans to health-related studies [16]. However it has been found that there should be a stronger link between the clinical trial phase of a drug and the PV monitoring system [5], [17]. In order to ensure that the niche PV system will allow for the most effective collection and evaluation of safety information, it is imperative that during the clinical trial phase the planning and operation of the PV system is taking into account. This entails considering if additional or more strenuous PV activities would need to be included [18]. Furthermore for the clinical trial and PV databases certain improvements are needed when addressing the timeliness, duplication, coverage and harmonization of the data collection [17].

PV 11. The system must be designed for niche specific conditions.

Code no	Requirements		Challenges							
	Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
PV 11	Niche environment specific	Specific populations/ patients need to be considered when setting up a pharmacovigilance system. Creating a single country-specific adverse event reporting form to be used by all.	Pediatrics, traditional medicines	-	Awareness, integrity of system	Laboratory, diagnostics	-	-	Consumers, pediatric, traditional medicine users	Confidentiality & ethics, adverse drug reactions detection

Although a PV system requires some form of standardisation in the reports it has come clear that the niche PV system still requires taking into account environment specific criteria [5]. When developing the niche PV system, it is necessary to take specific populations/ patients (such as paediatric patients, pregnant patients, elderly patients, and traditional medicine users) into account through the entire process i.e. the reporting phase, evaluation, and taking action and informing the customers [5].

As previously mentioned the use of traditional medicines are growing and thus it is imperative that these traditional medicines are incorporated into the PV system and other regulatory frameworks as there are certain safety concerns [11], [19].

Furthermore although there should be standardisation in developing an ADR report, the niche PV system also requires to create a single country-specific ADR report [7].

PV 12. A more proactive reporting process is required.

Code no	Requirements		Challenges							
	Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
PV 12	Reporting process	A more proactive approach with regards to reporting needs to be taken.	Adverse drug reactions, drug adherence	-	Late initiation, lack of reporting, awareness, poor healthcare system	-	Pharmacovigilance Culture	-	Doctors, pharmacists, consumers, pharmaceutical companies, limited resources, lack of finances	Under reporting, adverse drug reaction detection
		Low cost reporting solutions at international standards are required.								
		ADR reporting must be compulsory for healthcare professionals.								

Spontaneous reporting methods are the most common method used with regards to ADR reporting, however from literature it has been gathered that a more proactive approach needs to be taken. This entails modernising the system and starting the process earlier. The main focus is to create a philosophy that is driven by improving safety rather than looking for harm [6]. Furthermore in order to improve the issue of under reporting it has been found that implementing compulsory reporting or providing some form of compensation is needed with in the healthcare system [7].

Thus, for the niche PV system to be effective the PV system/ reporting process needs to be more proactive and healthcare workers need to play a more active role.

PV 13. Drug labels must be clear, readable, unambiguous and contain all the necessary information.

Code no	Requirements		Challenges							
	Requirement group	Defined	Supply & Distribution	Quality	Monitoring	Testing	PV Culture	PV Education	Stakeholder Involvement	Reporting & Process
PV 13	Drug labels	Drug labels must be visible, readable and easy to identify by consumers and health care workers especially the section on ADRs.	-	Quality, labelling	-	-	-	-	Doctors,	-

Drug labels should be clear, readable, unambiguous and contain all the necessary information regarding the drugs and the ingredients [20]. According to the standards of GMP the drug labels need to contain the name of the medicine, list of active ingredients³, expire date, storages and usages directions, and the name of the manufactures (pharmaceutical company) [20].

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³ The components of a pharmaceutical drug that provides the pharmacologic activities.

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4. Addendum A

Factor	Code no	Requirements		Challenges ²							
		Requirement group	Defined	Supply & Distribution ^A	Quality ^B	Monitoring ^C	Testing ^D	PV Culture ^E	PV Education ^F	Stakeholder Involvement ^G	Reporting & Process ^H
M	PV 1	Pharmacovigilance education should form an integral part of the system	Pharmacovigilance education needs to be incorporated into the health care system.								
			Pharmacovigilance needs to be introduced in undergraduate and graduate levels of teaching. Qualified personnel have to be in charge of pharmacovigilance within the different sectors.	Specialised drugs, paediatrics, traditional medicines, adverse drug reactions, drug adherence	-	Lack of reporting, late initiation, awareness	-	Pharma-covigilance Culture	Lack of KAP (Knowledge, Attitude and Practices), lack of training, insufficient curriculum	Government, Pharmacist, doctors, consumers	Adverse drug reactions detection, under reporting, quality of data
			Knowledge on the safety profile of medicines have to be increased within the healthcare system.								
	PV 2	Effective system	Pharmaceutical companies need to have trained staff.								
			A reporting system with ADR reporting forms need to exist. The PV plan should take into account risk identification during product development and risk management.	-	-	record keeping, poor healthcare system	laboratory, diagnostics	PV culture	Lack of KAP, lack of training, curriculum	Doctors, pharmacists, pharmaceutical companies	ADR detection, confidentiality & ethics, communication, quality of data
			A national PV centre needs to exist with designated staff and roles and well defined structure.								
	PV 3	Quality control	A PV advisory committee needs to exist and assist on technical matters.								
			Regular audits & inspections of pharmaceutical companies by healthcare workers need to be implemented. Quality management and control systems need to be implemented.	Specialised drugs, paediatrics, traditional medicines	Counterfeit, sub-standard, labelling	-	-	-	-	Consumers	Quality of data
	PV 4	Communication	Clear lines of communication have to exist between the different stakeholders within the healthcare system.	Specialised drugs, paediatrics, traditional medicines, shortages, stock-outs	counterfeit, substandard	Late initiation	laboratory, diagnostics	-	-	Government, Pharmaceutical companies Pharmacist, Doctors, Consumers	Quality of data, confidentiality & ethics, communication
			Stakeholders roles need to be defined clearly. All organizations involved with PV needs to embrace the concept of quality control and have a collaborative, transparent proactive behaviour.								
	PV 5	Defining stakeholders roles	Pharmaceutical companies need to be involved in PV and ADR reporting.	Drug-drug interaction, ADR, drug adherence, drug resistance	quality	Integrity of the system, lack of reporting, poor health systems, Awareness	-	PV culture	lack of KAP, lack of training	Government, Doctors, pharmacists, consumers, limited resources, Pharmaceutical companies	Under reporting, quality of data, confidentiality & ethics, communication
			Pharmaceutical companies need to have trained staff.								
	PV 6	Public/consumer involvement	Some form of public awareness on PV needs to be incorporated into the system.	Specialised drugs, paediatrics, traditional medicines, ADRs, drug resistance	-	Awareness, lack of reporting	laboratory, diagnostics	PV culture	Lack of KAP, lack of training, curriculum	consumers, pediatric, traditional limited resources, limited funding	ADR detection, communication, confidentiality & ethics, under reporting
			Patients need to receive feedback after reporting an ADR								
	PV 7	Databases	There must be a clinical trial and post-marketing database for specific drug roll-outs.								
			Computer systems used for PV should be validated and included the use of safety information outside drug safety functions (call centres). Database for the collecting and managing of ADRs needs to exist. Using literature to identify cases.	-	quality	record keeping, poor healthcare system, lack of reporting	-	-	-	Government, Doctors, pharmacists, consumers, limited resources, Pharmaceutical companies	Quality of data, ADR detection, Confidentiality & Ethics, Communication
	PV 8	Niche environment specific	Specific populations/ patients need to be considered when setting up a PV system.	paediatrics	-	awareness, integrity of system	laboratory, diagnostics	-	-	Consumers, pediatric, traditional	confidentiality & ethics, ADR detection
			Creating a single country-specific adverse event reporting form to be used by all.	Specialised drugs, paediatrics, traditional medicines, ADRs, drug adherence, drug resistance	quality, sub-standard, counterfeit	Awareness, lack of reporting, poor health systems, late initiation	-	-	-	Consumers, pediatric, traditional, doctor, pharmacists	ADR detection, communication, quality of data
	PV 9	ADR reports	Reports need to contain all relevant information and if important info is omitted, a system must be in place to contact reporter/healthcare unite to verify the case.								
			Special attention needs to be placed on drugs that are suspected for defects.								
	PV 10	Special drugs	Certain drug safety aspects need to be incorporated such as drug interactions and assessing the contribution of 'inactive' ingredients. Additional monitoring is required for new released drugs. Necessary that traditional medicines incorporated into national PV programmes.	Specialised drugs, paediatrics, traditional medicines, drug-drug interactions, ADRs	quality, sub-standard, counterfeit	Late initiation, record keeping	laboratory, diagnostics	-	-	consumers, pediatric, traditional	quality of data
			Generic drugs must be treated as a new released drug and follow all the necessary safety reporting requirements.								
	PV 11	Reporting process	A more proactive approach with regards to reporting needs to be taken.	ADR, drug adherence	-	Late initiation, lack of reporting, awareness, poor healthcare system	-	PV culture	-	Doctors, pharmacists, pharmaceutical companies, limited resources, lack of finances	Under reporting, ADR detection
			Low cost reporting solutions at international standards are required. ADR reporting must be compulsory for healthcare professionals.								
	PV 12	Link to clinical trials	In clinical trials, improvements in the mode of safety data collection, timelines, duplication, harmonization, and coverage need to be explored.								
			Drug labels must be visible, readable and easy to identify by consumers and health care workers especially the section on ADRs.	-	Quality, labelling	-	-	-	-	Doctors,	-

4

⁴ These challenges refer to all the challenges identified through systematic literature reviews that the factors (MPP, specific illnesses, RLS and traditional PV systems) attribute to and that the niche PV system needs to address. A total of 8 challenges groups were identified, listed A-H and a total of 43 challenges were identified. A shorted list is provided below.

A – **Supply & distribution:** Specialized drugs, pediatric drugs, traditional medicines, supply, shortages, stock-outs, drug-drug interactions (as a change in the effect of the drug when it is taken together with another drug and it can often lead to ADR), adverse drug reactions (any response to a drug which is noxious and unintended), drug adherence (the act where patients abide to the recommendations made regarding the dosage, timing and frequency of medication taken), drug resistance (the response to a drug in a susceptible parasite population decreases significantly)

B – **Quality:** Quality, dosages, labelling, counterfeit drugs (medical products that deliberately/fraudulently misrepresent their identity, composition or source), sub-standard drugs (authorized medical products that fail to meet either their quality standards or specifications, or both)

C – **Monitoring:** Integrity of the system (the support, integrity and confidentiality of the health care workers has seen to have an impact on treatment), record keeping, late initiation, lack of reporting, poor health system, awareness (lack of awareness and knowledge regarding the illness and treatment procedures)

D – **Testing:** Laboratory (the poor and limited amount of laboratories and testing infrastructures), diagnostics (diagnostic testing is required to predict the correct treatment procedure)

E – **PV Culture**

F – **Lack of education:** KAP (knowledge, attitude and Practices associated with PV), training (lack of effective PV training programs for healthcare professions), curriculum (incorporate PV subjects into the curriculum of healthcare students)

G – **Stakeholder involvement:** Government, lack of resources (people, time and money) lack of finances, pharmaceutical companies, pharmacists, doctors, consumers, pediatric/pregnant, traditional medicine users

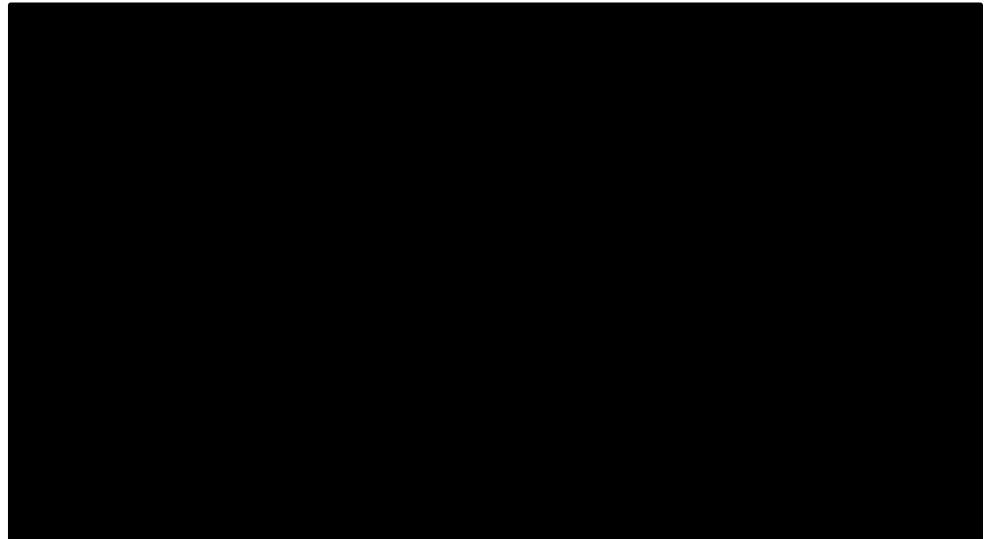
H – **Reporting & process:** Adverse drug reaction detection (identification of ADRs together with the detection of the connection between the ADRs and the drug exposure), confidentiality & ethics (trusting the healthcare workers), under reporting of ADRs, quality of data (the data gathered from reporting should be of a high quality), communication (communication platforms between the different stakeholders have to exist)

Validation of 'Niche Pharmacovigilance System' requirement specification related to pharmacovigilance.

Questionnaire

Biancé Huysamen

Health Systems Engineering and Innovation Hub
Department of Industrial Engineering, Faculty of Engineering
Stellenbosch University, South Africa



1. Introduction

As mentioned in the pre-read document the 'Niche Pharmacovigilance System' addresses 4 factors namely current pharmacovigilance systems, the Medicine Patent Pool, resource limited settings, and specific illnesses (HIV, TB and Hepatitis C). However for the purpose of this questionnaire focus was placed on the unique requirements that the current pharmacovigilance system factor would call for in the Niche Pharmacovigilance Systems. This questionnaire is aimed at improving, adjusting and establishing the importance of the requirements called for by current pharmacovigilance systems.

Please complete the following personal details

**Kindly note that the participant's personal information is required only for reference purposes and will not appear in the thesis document or in any published work.*

Name:

Email address:

Professional Background:

Organisation:

Experience in this field:

- ☐ Highly experienced
☐ Moderately experienced
☐ Some experience

2. Pharmacovigilance related requirement specification

In the pre-read document the 13 requirements identified related to pharmacovigilance are provided along with a description and a breakdown of how these requirements address challenges identified in the pharmaceutical value chain.

2.1. Rating the relevance of the requirements

Rate the 13 requirements (numbered PV1 - PV13) need to be rated with regards to the relevance to the contribution of the Niche Pharmacovigilance System using the following Likert scale.

- 1 - Strongly disagree
 2 - Disagree

3 - More or less disagree

4 - Neutral

5 - More or less agree

6 - Agree

7 - Strongly agree

Code	Requirement	Relevance rating						
		1	2	3	4	5	6	7
PV1	Pharmacovigilance education needs to form an integral part of the system.							
	<i>Additional comments related to PV1</i>							
PV2	Clear lines of communication have to exist within the system.							
	<i>Additional comments related to PV2</i>							
PV3	The system requires public/consumer involvement.							
	<i>Additional comments related to PV3</i>							
PV4	The system requires an effective database for the collecting and managing of reports.							
	<i>Additional comments related to PV4</i>							
PV5	A pharmacovigilance centre or reporting system needs to exist.							
	<i>Additional comments related to PV5</i>							
PV6	The system requires effective quality management and quality control systems.							
	<i>Additional comments related to PV6</i>							
PV7	The stakeholders' roles need to be clearly defined.							
	<i>Additional comments related to PV7</i>							
PV8	ADR reporting forms need to contain all relevant information.							
	<i>Additional comments related to PV8</i>							
PV9	More care should be taken with specialized drugs.							
	<i>Additional comments related to PV9</i>							

PV10	A link needs to exist between pharmacovigilance systems and clinical trials.								
	<i>Additional comments related to PV10</i>								
PV11	The system must be designed for niche specific conditions.								
	<i>Additional comments related to PV11</i>								
PV12	A more proactive reporting process is required.								
	<i>Additional comments related to PV12</i>								
PV13	Drug labels must be clear, readable, unambiguous and contain all the necessary information.								
	<i>Additional comments related to PV13</i>								

2.2. Are there any additional requirements that you would include?

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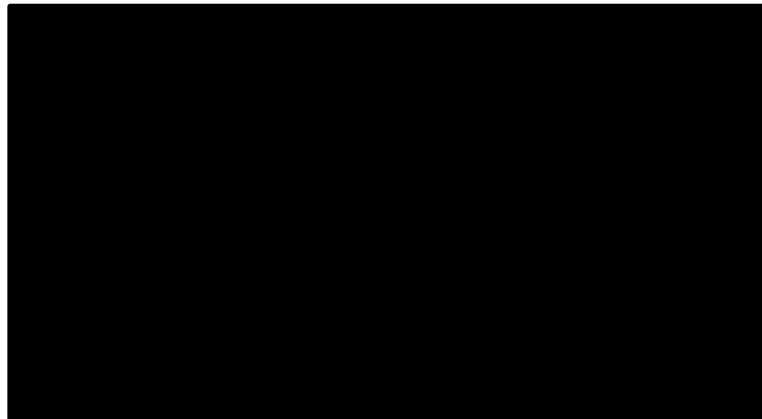
E.2. MPP related requirement validation documents

**Validation of 'Niche Pharmacovigilance
System' requirement specification related to
the Medicine Patent Pool.**

Questionnaire

Biancé Huysamen

Health Systems Engineering and Innovation Hub Department
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Stellenbosch University, South Africa



1. Introduction

As mentioned in the pre-read document the 'Niche Pharmacovigilance System' addresses 4 factors namely current pharmacovigilance systems, the Medicine Patent Pool, resource limited settings, and specific illnesses (HIV, TB and Hepatitis C). However, for the purpose of this questionnaire focus was placed on the unique requirements that the Medicine Patent Pool factor would call for in the Niche Pharmacovigilance Systems. This questionnaire is aimed at improving, adjusting and establishing the importance of the requirements called for by current pharmacovigilance systems.

Please complete the following personal details

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Name:

Email address:

Professional Background:

Organization:

Experience in this field:

- ☐ Highly experienced
☐ Moderately experienced
☐ Some experience

2. Medicine Patent Pool related requirement specification

In the pre-read document, the 8 requirements identified related to the Medicine Patent Pool are provided along with a description and a breakdown of how these requirements address challenges identified in the pharmaceutical value chain.

2.1. Rating the relevance of the requirements

Using a Likert scale each of the 8 requirements (numbered MPP1 - MPP8) need to be rated with regards to the relevance to the contribution of the Niche Pharmacovigilance System.

- 1 - Strongly disagree
 2 - Disagree

3 - More or less disagree

4 - Neutral

5 - More or less agree

6 - Agree

7 - Strongly agree

Code	Requirement	Relevance rating						
		1	2	3	4	5	6	7
MPP1	Pharmacovigilance education needs to form an integral part of the system. This entails educating pharmaceutical companies on pharmacovigilance.							
	<i>Additional comments related to MPP1</i>							
MPP2	Clear lines of communication have to exist within the system.							
	<i>Additional comments related to MPP2</i>							
MPP3	Proper funding systems should be in place to improve infrastructures for drug monitoring systems.							
	<i>Additional comments related to MPP3</i>							
MPP4	The reporting system must be able to locate adverse drug reactions promptly and ensure effective storage of the reports.							
	<i>Additional comments related to MPP4</i>							
MPP5	The stakeholders' roles need to be clearly defined.							
	<i>Additional comments related to MPP5</i>							
MPP6	Effective quality control systems have to be in place in the different areas of the pharmacovigilance system.							
	<i>Additional comments related to MPP6</i>							
MPP7	Drug labels must be clear, readable, unambiguous especially the section on adverse drug reactions.							
	<i>Additional comments related to MPP7</i>							
MPP8	The system must be designed for niche specific conditions.							
	<i>Additional comments related to MPP8</i>							

2.2. Are there any additional requirements that you would include?

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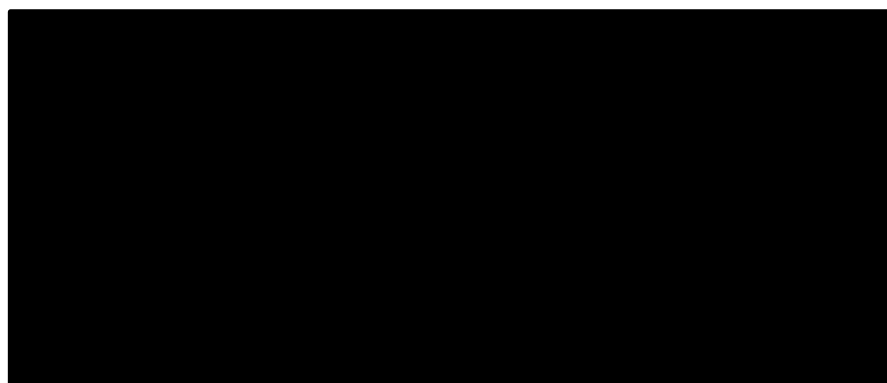
E.3. RLS related requirements validation documents

**Validation of 'Niche Pharmacovigilance
System' requirement specification related to
resource limited settings.**

Questionnaire

Biancé Huysamen

Health Systems Engineering and Innovation Hub Department
of Industrial Engineering, Faculty of Engineering
Stellenbosch University, South Africa



1. Introduction

As mentioned in the pre-read document the 'Niche Pharmacovigilance System' addresses 4 factors namely current pharmacovigilance systems, the Medicine Patent Pool, resource limited settings, and specific illnesses (HIV, TB and Hepatitis C). However, for the purpose of this questionnaire focus was placed on the unique requirements that resource limited settings factor would call for in the Niche Pharmacovigilance Systems. This questionnaire is aimed at improving, adjusting and establishing the importance of the requirements called for by current pharmacovigilance systems.

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Name:

Email address:

Professional Background:

Organization:

Experience in this field:

- ☐ Highly experienced
☐ Moderately experienced
☐ Some experience

2. Resource limited settings related requirement specification

In the pre-read document the 9 requirements identified related to resource limited settings are provided along with a description and a breakdown of how these requirements address challenges identified in the pharmaceutical value chain.

2.1. Rating the relevance of the requirements

Using a Likert scale each of the 9 requirements (numbered RLS1 - RLS9) need to be rated with regards to the relevance to the contribution of the Niche Pharmacovigilance System.

- 1 - Strongly disagree
 2 - Disagree

3 - More or less disagree

4 - Neutral

5 - More or less agree

6 - Agree

7 - Strongly agree

Code	Requirement	Relevance rating						
		1	2	3	4	5	6	7
RLS1	Pharmacovigilance education and capacity building need to form an integral part of the system.							
	<i>Additional comments related to RLS1</i>							
RLS2	Additional and more active reporting methods are required.							
	<i>Additional comments related to RLS2</i>							
RLS3	A link needs to exist between pharmacovigilance systems and clinical trials.							
	<i>Additional comments related to RLS3</i>							
RLS4	Clear lines of communication have to exist within the system.							
	<i>Additional comments related to RLS4</i>							
RLS5	The system requires public/consumer involvement.							
	<i>Additional comments related to RLS5</i>							
RLS6	The system needs to be region specific and take the specific environments' needs into account.							
	<i>Additional comments related to RLS6</i>							
RLS7	The reporting process must be able to operate with limited resources							
	<i>Additional comments related to RLS7</i>							
RLS8	Reporting should be made compulsory or some form of remuneration should be granted to healthcare workers when they report adverse drug reactions							
	<i>Additional comments related to RLS8</i>							
RLS9	The Government should play an integral part of the pharmacovigilance system and some form of a national strategy should be implemented.							
	<i>Additional comments related to RLS9</i>							

2.2. Are there any additional requirements that you would include?

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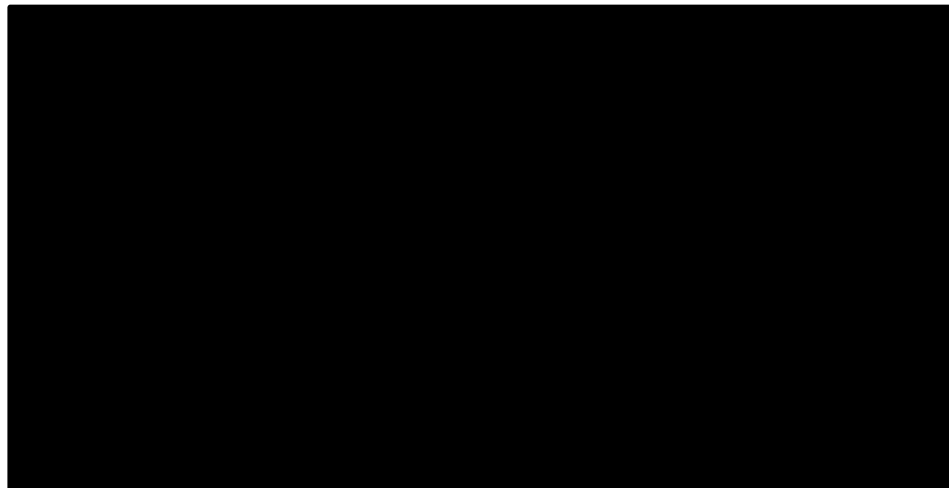
E.4. HIV, TB and Hepatitis C related requirements validation documents

**Validation of 'Niche Pharmacovigilance
System' requirement specification related to
specific illnesses (HIV, TB and Hepatitis C).**

Questionnaire

Biancé Huysamen

Health Systems Engineering and Innovation Hub Department
of Industrial Engineering, Faculty of Engineering
Stellenbosch University, South Africa



1. Introduction

As mentioned in the pre-read document the 'Niche Pharmacovigilance System' addresses 4 factors namely current pharmacovigilance systems, the Medicine Patent Pool, resource limited settings, and specific illnesses (HIV, TB and Hepatitis C). However for the purpose of this questionnaire focus was placed on the unique requirements that the specific illness factor would call for in the Niche Pharmacovigilance Systems. This questionnaire is aimed at improving, adjusting and establishing the importance of the requirements called for by specific illnesses

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Name:

Email address:

Professional Background:

Organization:

Experience in this field:

- ☐ Highly experienced
☐ Moderately experienced
☐ Some experience

2. Resource limited settings related requirement specification

In the pre-read document, the 9 requirements identified related to pharmacovigilance are provided along with a description and a breakdown of how these requirements address challenges identified in the pharmaceutical value chain

2.1. Rating the relevance of the requirements

Using a Likert scale each of the 9 requirements (numbered SI1 - SI9) need to be rated with regards to the relevance to the contribution of the Niche Pharmacovigilance System.

- 1 - Strongly disagree
 2 - Disagree

3 - More or less disagree

4 - Neutral

5 - More or less agree

6 - Agree

7 - Strongly agree

Code	Requirement	Relevance rating						
		1	2	3	4	5	6	7
SI1	Pharmacovigilance education needs to form an integral part of the system and should incorporate knowledge on specific illnesses.							
	<i>Additional comments related to SI1</i>							
SI2	More active monitoring systems and additional methods and techniques have to be incorporated.							
	<i>Additional comments related to SI2</i>							
SI3	Reports need to be standardized but should still be illness specific.							
	<i>Additional comments related to SI3</i>							
SI4	The system needs to take the environment' conditions into account.							
	<i>Additional comments related to SI4</i>							
SI5	More care needs to be taken with vulnerable patients.							
	<i>Additional comments related to SI5</i>							
SI6	Stakeholders' roles need to be clearly defined.							
	<i>Additional comments related to SI6</i>							
SI7	The system should be designed to take into account specialized drugs.							
	<i>Additional comments related to SI7</i>							
SI8	The system requires proper quality management and control systems to be in place.							
	<i>Additional comments related to SI8</i>							
SI9	Public awareness should form an integral part of the system and should be targeted at specific patient populations.							
	<i>Additional comments related to SI9</i>							

2.2. Are there any additional requirements that you would include?

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Appendix F. Additional information related to the CVSIT

Appendix F provides additional information regarding the developed tool, the CVSIT.

The following sections are included:

F1: Inclusion/ exclusion criteria of the intervention strategies

F2: Dimensions of the CVSIT in excel-base

F2.1. Dimension 1

F2.2. Dimension 2

F2.3. Dimension 3

F2.4. Dimension 4

F3: Detailed level process map and background logic for CVSIT

F.1. Inclusion/ exclusion criteria of intervention strategies

In this section the inclusion/ exclusion criteria for the intervention strategies, as depicted in the Vigilance system implementation landscape, is provided. The criteria sets are used during the development of the CVSIT, in order to establish what project related information, within the context of the environment, i.e. the infrastructure, resources etc., would be required in order to determine which of the intervention strategies are applicable to a project. This criteria set is based of the Vigilance system implementation landscape and relevant literature and is summarised in Table F.1.

Table F.1: Inclusion/exclusion criteria of intervention strategies for CVSIT development

Intervention strategy	Inclusion/exclusion criteria with respect to environment (i.e. the infrastructure and resources)	Domain
Component 1: Mode of reporting		
Mobile application	Resources assisting with reporting or operating of the drug safety system i.e. HCP such as doctors, pharmacists, nurses and/or other PV experts, need to have a low/rudimental level of experience with regards to drug safety systems and identifying of ADRs (Aranda-Jan, Mohutsiwa-Dibe and Loukanova, 2014).	Human resources
	Requires access to a cellular network (Politi, 2001; Bradshaw, 2013) Requires the reporting facility to have access to handheld devices for the function of reporting (Politi, 2001; Mechael, 2009; Aranda-Jan, Mohutsiwa-Dibe and Loukanova, 2014; Kuchya <i>et al.</i> , 2016)	Technology resource
Paper-based	<i>No specific requirement with respect to infrastructure is required</i> (Almenoff, 2007)	—
Text-based	Requires that patient have knowledge on identification of ADRs and the reporting process (Baron <i>et al.</i> , 2013).	Patient information
	Resources operating drug safety system i.e. doctors, pharmacists, nurses and/or other PV experts need to have a low/ rudimental level of experience with regards to drug safety systems (Aranda-Jan, Mohutsiwa-Dibe and Loukanova, 2014).	Human resources
	Requires access to a cellular network (Politi, 2001; Bradshaw, 2013) Requires the reporting facility to have access to handheld devices for the function of reporting (Politi, 2001; Mechael, 2009; Aranda-Jan, Mohutsiwa-Dibe and Loukanova, 2014; Kuchya <i>et al.</i> , 2016)	Technology resources
Web-based	Requires that resources i.e. doctors, pharmacists, nurses and/or other PV experts, that assist with ADR reporting have a rudimental level of experience with regards to drug safety systems (Edwards, 2019; Medicines & Healthcare Agency Regulatory (MHRA), 2019)	Human resources
	This intervention strategy requires the reporting facility to have access to the Internet, network connection (Gibb, 2016; Summerfield, 2019) This intervention strategy requires the reporting facility to have access to a desktop or handheld devices for the function of reporting (Politi, 2001; Medicines & Healthcare Agency Regulatory (MHRA), 2019)	Technology resources
Component 2: Reporting process		
3-step approach	The patient(s) must visit a healthcare facility/ health care practitioner for the reporting of ADRs (Mudzviti <i>et al.</i> , 2013)	Technology resources

	Requires a moderate availability of nurses or/and interns to assist with the reporting process (if other HCP are not available) (Mudzviti <i>et al.</i> , 2013) Resources operating drug safety system, i.e. nurses and/or other interns, need to have a low level of experience with regards to drug safety systems (Mudzviti <i>et al.</i> , 2013)	Human resources
Black triangle monitoring	This intervention requires the project to focus on one specific drug (Martin <i>et al.</i> , 1998; European Medicines Agency, 2013) Requires to be implemented for the reporting and monitoring of newly released drug(s)/ or drugs that need to be monitored more intensively (Martin <i>et al.</i> , 1998; European Medicines Agency, 2013)	Project information
	Resources operating drug safety system i.e. doctors, pharmacists, and/or other PV experts need to have a high level of experience with regards to drug safety systems (Martin <i>et al.</i> , 1998).	Human resources
CEM	Requires the project to focus on one specific drug (Wallberg, 2009; Pal <i>et al.</i> , 2013)	Project information
	This intervention strategy requires the project to focus on a finite, pre-defined patient group (Wallberg, 2009; Pal <i>et al.</i> , 2013; Dodoo <i>et al.</i> , 2014) Requires that the patients visit a healthcare facility/ health care practitioner for continuous evaluation and reporting of ADRs (Wallberg, 2009; Pal <i>et al.</i> , 2013; Dodoo <i>et al.</i> , 2014)	Patient information
	This intervention strategy requires moderate availability of human resources, i.e. doctors, pharmacists, nurses, or other PV experts, to operate the reporting system (Wallberg, 2009; Pal <i>et al.</i> , 2013; Dodoo <i>et al.</i> , 2014)(Kunak <i>et al.</i> , 2015) Requires that resources assisting with the identification and reporting of ADRs during the CEM have a rudimentary level of experience with regards to drug safety systems (Edwards, 2019)	Human resources
Designated PV person	The project should be targeted at a specific set of healthcare facilities (Rachlis <i>et al.</i> , 2016; Edwards, 2019).	Project information
	Requires high level of availability of human resources, i.e. doctors, pharmacists, nurses, or other PV experts, to operate the reporting system (Rachlis <i>et al.</i> , 2016; Edwards, 2019). Resources operating drug safety and reporting system need to have a high level of experience with regards to drug safety systems (Rachlis <i>et al.</i> , 2016; Edwards, 2019).	Human resources
PDR	The patient would require to have knowledge on identification of ADRs and the reporting process (Anderson <i>et al.</i> , 2011; Delaney, 2017).	Patient information
	Patients are required to have access to a cellular network or the Internet (Anderson <i>et al.</i> , 2011; Delaney, 2017) The patients are required to have access to mobile devices or desktops (Anderson <i>et al.</i> , 2011; Delaney, 2017)	Technology resource availability
Sentinel surveillances	Requires that the project to focus on one specific drug/ disease (Management Sciences for Health (MSH), 2010; Olsson <i>et al.</i> , 2010; Miller, Nwokike and Stergachis, 2012). The project should be targeted at a specific set of healthcare facilities (Management Sciences for Health (MSH), 2010; Olsson <i>et al.</i> , 2010).	Project information
	Requires that the project to focus on a finite, pre-defined patient group (Management Sciences for Health (MSH), 2010). The patient(s) would be required to visit a healthcare facility/ health care practitioner for continuous evaluation and reporting of ADRs (Management Sciences for Health (MSH), 2010; Olsson <i>et al.</i> , 2010).	Patient information
	Requires moderate availability of resources, i.e. doctors, pharmacists, nurses, or other PV experts, to assist with the reporting and monitoring process (Miller, Nwokike and Stergachis, 2012) Resources required to have a high level of experience with regards to drug safety systems (Miller, Nwokike and Stergachis, 2012)	Human resources
Spontaneous reporting	Requires limited availability of HCP, i.e. doctors, pharmacists, nurses, interns or other PV experts, to assist with reporting of ADRs (Pal <i>et al.</i> , 2013; Masenyetse, Manda and Mwambi, 2015)	Human resources
Task shifting	The patient(s) would be required to visit a healthcare facility/ health care practitioner for the reporting of ADRs (WHO, 2007b; Olsson, Pal and Dodoo, 2015a; Prasad <i>et al.</i> , 2018).	Patient information

		Requires a moderate availability of nurses or/and interns to assist with the reporting process if doctors, pharmacists and/or other HCP have limited availability (WHO, 2007b; Olsson, Pal and Dodoo, 2015a; Prasad <i>et al.</i> , 2018) Resources i.e. nurses and/or other interns, required to have a low level of experience with regards to drug safety systems (WHO, 2007b; Olsson, Pal and Dodoo, 2015a; Prasad <i>et al.</i> , 2018)	Human resources
TSR		Requires the project to focus on one specific drug/ disease (Pal <i>et al.</i> , 2013; Ndagije, Nambasa and Namagala, 2015).	Project information
		Requires the project to focus on a finite, pre-defined patient group (Pal <i>et al.</i> , 2013; Ndagije, Nambasa and Namagala, 2015).. The patient(s) would be required to visit a healthcare facility/ health care practitioner for continuous evaluation and reporting of ADRs (Pal <i>et al.</i> , 2013; Prasad <i>et al.</i> , 2018)	Patient information
		Requires moderate availability of resources, i.e. doctors, pharmacists, nurses, or other PV experts, to assist with monitoring and reporting of ADRs (Pal <i>et al.</i> , 2013; Prasad <i>et al.</i> , 2018). Resources operating drug safety system i.e. doctors, pharmacists, nurses and/or other PV experts need to have a high level of experience with regards to drug safety systems (Pal <i>et al.</i> , 2013; Prasad <i>et al.</i> , 2018).	Human resources
Component 3: Database			
Individual databases		This intervention strategy should be considered if the project requires a dedicated database (a database for their own use) gathered (WHO and The Global Fund, 2010; Chakrabarty and Thawani, 2011)	Project information
		Requires moderate availability of human resources, i.e. doctors, pharmacists, or other PV experts, to operate the database (WHO and The Global Fund, 2010; Chakrabarty and Thawani, 2011).. Resources operating drug safety system required to have a limited level of experience with regards to drug safety systems (WHO and The Global Fund, 2010; Chakrabarty and Thawani, 2011).	Human resources
		Requires the reporting facility to have access to a desktop for the purpose of data-capturing requires access to data processing software (WHO and The Global Fund, 2010; Chakrabarty and Thawani, 2011).	Technology resources
Outsourcing		Resources assisting with the database quires a limited level of experience and availability with regards to drug safety data monitoring as the operations of the data process is outsourced (Edwards, 2008; Arora, 2012)	Human resources
		This intervention requires access to the Internet in order to gain access to the real-time data from the provider (Edwards, 2008; Arora, 2012; Oracle, 2018; PrimeVigilance, 2019)	Technology access
Physical storage		Requires that the reporting forms need to be stored in a safe space once they have been uploaded to the specific database (Almenoff, 2007; SCOPE and MHRA, 2015)	Project information
VigiBase		Resources, HCP, required need to have a limited level of experience with regards to drug safety systems and entering of data into the VigiBase system (Lindquist, 2008; UMC, 2019b)	Human resources
		This intervention strategy requires the reporting facility to have access to the Internet for the purpose of entering the data in VigiBase (Lindquist, 2008; Gibb, 2016; Summerfield, 2019; UMC, 2019b) This intervention strategy requires the reporting facility to have access to a device for the purpose of data-capturing and entering of the data into VigiBase(Politi, 2001; Lindquist, 2008; UMC, 2019b)	Technology resources
Component 4: Response strategy			
App Alerts		This intervention strategy requires the reporting facility to have access to a cellular network or to the Internet (Politi, 2001; Bradshaw, 2013; Edwards, 2019; Walker, 2019) This intervention strategy requires the reporting facility to have access to handheld devices (Politi, 2001; Kuchya <i>et al.</i> , 2016; Edwards, 2019; Walker, 2019)	Technology resources
Feedback	Mobile application	Requires the reporting facility to have access to a cellular network (Politi, 2001; Bradshaw, 2013) Requires the reporting facility to have access to handheld devices for the purpose of communication & feedback (Politi, 2001; Bradshaw, 2013)	Technology resources
	Email	Requires the reporting facility to have access to a cellular network or the Internet (Politi, 2001; Bradshaw, 2013; Gibb, 2016; Summerfield, 2019) Requires the reporting facility to have access to handheld devices or desktop for the purpose of communication & feedback (Politi, 2001; Bradshaw, 2013)	Technology resources

	Web-based	Requires the reporting facility to have access to a cellular network or the Internet (Politi, 2001; Bradshaw, 2013) (Gibb, 2016; Summerfield, 2019) Requires the reporting facility to have access to handheld devices or desktop for the purpose of communication & feedback (Politi, 2001; Bradshaw, 2013)	Technology resources
	Paper-based	<i>No specific requirement with respect to infrastructure or resources is required</i> (Almenoff, 2007; Vermeir <i>et al.</i> , 2015)	-
Policy & guidelines		<i>No specific requirement with respect to infrastructure or resources is required</i> (WHO, 2002c; Mehta, Allen, <i>et al.</i> , 2014)	-
Component 5: Awareness			
Campaigns		For this intervention strategy to be effective the project should focus on creating a culture of drug safety reporting in addition to reporting of ADRs. (Lamprecht, Bam and De Kock, 2017) (Steurbaut and Hanssens, 2014)	Project information
Collaboration & partnerships		For this intervention strategy to be effective the project should focus on creating a culture of drug safety reporting in addition to reporting of ADRs (Lamprecht, Bam and De Kock, 2017) (Schito <i>et al.</i> , 2015).	Project information
Communities of practices		<i>No specific requirement with respect to infrastructure or resources is required</i> (Dennison, Wu and Ickes, 2014).	-
Paper-based		<i>No specific requirement with respect to infrastructure or resources is required</i> (Almenoff <i>et al.</i> , 2007; Ilic and Rowe, 2013)	-
Social media		This intervention strategy requires the reporting facility to have access to a cellular network or the Internet (Politi, 2001; Bradshaw, 2013; Sloane, Osanlou and Lewis, 2015; Gibb, 2016; Summerfield, 2019) This intervention strategy requires the reporting facility to have access to a desktop or handheld devices (Politi, 2001; Bradshaw, 2013; Gibb, 2016; Summerfield, 2019). The patient(s) are required to have access to a cellular network or the Internet (Sloane, Osanlou and Lewis, 2015). The patient(s) are required to have access to mobile devices or desktops (Politi, 2001; Bradshaw, 2013) (Gibb, 2016; Summerfield, 2019)	Technology resources
Component 6: Communication			
Communication plans		<i>No specific requirement with respect to infrastructure or resources is required</i> (Bahri, 2010).	-
ICTs	Requires limited availability of resources, i.e. HCP doctors, pharmacists, nurses, interns or other PV experts, to assist with the communication of ADR reports, actions to take with respect to the ADR etc (Lu, 2009).		Human resources
	Requires the reporting facility to have access to a cellular network or the Internet for communication purposes (Politi, 2001; Gichoya, 2005; Bradshaw, 2013; Aranda-Jan, Mohutsiwa-Dibe and Loukanova, 2014) Requires the reporting facility to have access to a desktop or handheld devices for communication purposes (Politi, 2001; Gichoya, 2005; Bradshaw, 2013; Aranda-Jan, Mohutsiwa-Dibe and Loukanova, 2014; Gibb, 2016; Summerfield, 2019)		Technology resources
Paper-based		Requires limited availability of resources, i.e. HCP doctors, pharmacists, nurses, interns or other PV experts, to assist with the communication of ADR reports, actions to take with respect to the ADR etc (Almenoff, 2007)	Human resources
Policy		<i>No specific requirement with respect to infrastructure or resources is required</i> (WHO, 2004; Bahri, 2010).	
Component 7: Educational			
Learning centres		The project should focus on creating a culture of drug safety reporting in addition to reporting of ADRs (Lamprecht, Bam and De Kock, 2017) (Gerritsen <i>et al.</i> , 2011; WHO, 2012)	Project information

	Requires there to be a facility for educational response and other activities in addition to the reporting of ADRs (WHO, 2012).	Resources
Paper-based	<i>No specific requirement with respect to infrastructure or resources is required</i> (Ilic and Rowe, 2013).	-
Patient information cards	<i>No specific requirement with respect to infrastructure or resources is required, however this intervention strategy should be considered when implementing PDR</i> (Poirot <i>et al.</i> , 2016).	-
PV curriculum	The project should focus on creating a culture of drug safety reporting in addition to reporting of ADRs, aimed at addressing the entire healthcare facility (Hagemann <i>et al.</i> , 2014; Hartman, Härmark and van Puijenbroek, 2017; Edwards, 2019).	Project information
	Requires limited/ moderate availability of resources, i.e. interns or students, to partake in the intervention by completing the curriculum (Hagemann <i>et al.</i> , 2014; Hartman, Härmark and van Puijenbroek, 2017; Edwards, 2019).	Human resources
Short courses	The project should focus on creating a culture of drug safety reporting in addition to reporting of ADRs, as resources would have to complete the course (Lamprecht, Bam and De Kock, 2017)	Project information
	Requires limited availability of human resources, i.e. doctors, pharmacists, nurses, interns or other PV experts, to be educated on the operations of drug safety monitoring by completing the course (Dunn and Thorogood, 2002).	Human resources
	Requires the reporting facility to have access to the Internet, in the case of e-learning (Dunn and Thorogood, 2002; Gibb, 2016; Summerfield, 2019; The Global Health Network, 2019a) Requires the reporting facility to have access to a desktop or handheld devices for educational purposes in the case of e-learning (Politi, 2001; Dunn and Thorogood, 2002; The Global Health Network, 2019a)	Technology resources
Social media	The project should focus on creating a culture of drug safety reporting in addition to reporting of ADRs (Edwards, 2019).	Project information
	Requires the reporting facility to have access to a cellular network or the Internet for educational purposes (Politi, 2001; Edwards and Lindquist, 2011; Bradshaw, 2013; Sloane, Osanlou and Lewis, 2015; Gibb, 2016; Summerfield, 2019) Requires the reporting facility to have access to a desktop or handheld devices for educational purposes (Politi, 2001; Edwards and Lindquist, 2011; Bradshaw, 2013; Gibb, 2016; Summerfield, 2019)	Technology resources
Web-based	Requires the reporting facility to have access to the Internet (Politi, 2001; Bradshaw, 2013; Gibb, 2016; Summerfield, 2019; The Global Health Network, 2019b; Walker, 2019) Requires the reporting facility to have access to a desktop for educational purposes (Politi, 2001; Bradshaw, 2013; The Global Health Network, 2019b; Walker, 2019)	Technology resources
Component 8: Quality management		
Addressing GMP & GDP	Requires limited availability of human resources, i.e. HCP, such as doctors, pharmacists, nurses, interns or other PV experts, to address the guidelines as stipulated in GMP & GDP (Pan American Health Organization, 2011; WHO, 2011)	Human resources
Audits	<i>No specific requirement with respect to infrastructure or resources is required</i> (Pietrek, Coulson and Czarnecki, 2009; Nwaiwu, Oyelade and Eze, 2016)	-
GVP	Requires limited availability of human resources, i.e. HCP, such as doctors, pharmacists, nurses, interns or other PV experts, to address the guidelines as stipulated in GVP (Pietrek, Coulson and Czarnecki, 2009; Pan American Health Organization, 2011; European Medicines Agency, 2017)	Human resources
Policy and guidelines	<i>No specific requirement with respect to infrastructure or resources is required</i> (WHO, 2002b, 2004; European Medicines Agency, 2017)	-
Component 9: Responsibility and accountability		
Career development	The project should focus on creating a culture of drug safety reporting in addition to reporting of ADRs (Weller, 2008; Gerritsen <i>et al.</i> , 2011; Lamprecht, Bam and De Kock, 2017)	Project information
	Requires moderate availability of human resources, i.e. doctors, pharmacists, nurses, interns or other PV experts, to partake in career development practices, i.e. education strategies (Weller, 2008; Gerritsen <i>et al.</i> , 2011)	Human resources

Designated PV person	The project should be targeted at a specific set of healthcare facilities (Rachlis <i>et al.</i> , 2016; Edwards, 2019).	Project information
	Requires high level of availability of human resources, i.e. doctors, pharmacists, nurses, or other PV experts, to operate the reporting system (Rachlis <i>et al.</i> , 2016; Edwards, 2019). Resources operating drug safety system i.e. doctors, pharmacists, nurses and/or other PV experts need to have a high level of experience with regards to drug safety systems (Rachlis <i>et al.</i> , 2016; Edwards, 2019). This intervention requires a dedicated person for the purpose of drug safety monitoring (Rachlis <i>et al.</i> , 2016; Edwards, 2019).	Human resources
Financial incentives	The project should focus on creating a culture of drug safety reporting in addition to reporting of ADRs(Weller, 2008; Gerritsen <i>et al.</i> , 2011; Lamprecht, Bam and De Kock, 2017)	Project information
Positive working environment	The project should focus on creating a culture of drug safety reporting in addition to reporting of ADRs(Weller, 2008; Gerritsen <i>et al.</i> , 2011; Lamprecht, Bam and De Kock, 2017)	Project information
Policy	<i>No specific requirement with respect to infrastructure or resources is required</i> (Mehta, Allen, <i>et al.</i> , 2014)	-
Workload management	This intervention strategy requires high availability of human resources, i.e. nurses or interns or other PV experts to assist doctors and other healthcare practitioners with ADR reporting (Weller, 2008; Elovainio, 2010).	Human resources
Component 10: Novel technologies		
Blockchain	Resources assisting with drug safety system within the context of blockchain need to have a rudimental - high level of experience based on specified roles (Price, 2018).	Human resources
	Requires the access to the Internet (or network for storage purposes) (Rosic, 2016; Elliot, 2018; Liang <i>et al.</i> , 2018; Price, 2018) Requires access to a desktop (or other hardware) for data capturing and data processing. Rosic, 2016; Elliot, 2018; Liang <i>et al.</i> , 2018; Price, 2018) Requires the project to have access to data processing software/ and data storage. Rosic, 2016; Elliot, 2018; Liang <i>et al.</i> , 2018; Price, 2018) The project should have the capability to invest into R&D with respect to novel technologies (Price, 2018).	Technology resources
Data mining	Resources assisting with the operating of the drug safety system have to have a rudimental level of experience with regards to drug safety systems. Also they would have to have a high level of experience with datamining or other related fields within data science (Cleland-Huang, 2015)	Human resources
	Requires access to the Internet, or other network services (Wilson, Thabane and Holbrook, 2004; Cleland-Huang, 2015; Engels <i>et al.</i> , 2016; Shukla, 2017; Wu <i>et al.</i> , 2017) Requires access to a hardware, such as desktop or laptop, for data capturing and data processing. Furthermore also requires access to data processing software, data storage and other related infrastructures, such as data operating systems(Wilson, Thabane and Holbrook, 2004; Cleland-Huang, 2015; Engels <i>et al.</i> , 2016; Shukla, 2017; Wu <i>et al.</i> , 2017) The project should have the capability to invest into R&D with respect to novel technologies (Cleland-Huang, 2015; Wu <i>et al.</i> , 2017)	Technology resources
Machine learning	Resources assisting with the operating of the drug safety system, within the context of machine learning have a rudimental level of experience with regards to drug safety systems. Also they would have to have a high level of experience with machine learning (Lee and Chen, 2019).	Human resources
	Requires the reporting facility to have access to the Internet or network for cloud storage purposes (Russom, 2018; Wiens and Shenoy, 2018; Lee and Chen, 2019; Singh, 2019) Access to a Hardware, such as desktop or laptop, for data capturing and data processing within the context of Machine learning. Furthermore it also requires access infrastructure for data management (i.e. data systems, processing software etc.) (Russom, 2018; Wiens and Shenoy, 2018; Lee and Chen, 2019; Singh, 2019) Access to large volumes of data, in order to develop the learning algorithms(Russom, 2018) The project should have the capability to invest into R&D with respect to novel technologies (Price, 2018; Lee and Chen, 2019)	Technology resources

Social Media	Resources assisting with the operating of the drug safety system, within the context of social media have a rudimentary level of experience with regards to drug safety systems. Also they would have to have a high level of experience with respect to data science (Nikfarjam <i>et al.</i> , 2015; Sloane, Osanlou and Lewis, 2015).	Human resources
	Requires the reporting facility to have access to a cellular network, the Internet or other networking system (Cleland-Huang, 2015; Nikfarjam <i>et al.</i> , 2015; Sloane, Osanlou and Lewis, 2015) Requires access to hardware and , such as desktop or laptop, for data capturing and data processing. Requires the project to have access to infrastructure for data management, i.e. data processing software, data system) (Cleland-Huang, 2015; Nikfarjam <i>et al.</i> , 2015; Sloane, Osanlou and Lewis, 2015) The project should have the capability to invest into R&D with respect to novel technologies (Nikfarjam <i>et al.</i> , 2015; Sloane, Osanlou and Lewis, 2015)	Technology resources

F.2. CVSIT Dimensions

In this section the different dimensions of the CVSIT in the excel based format is provided. There are four subsections related to the four different dimensions, dimension1 - vigilance profile assessment, dimension 2 – Vigilance System Component-Intervention Index, dimension 3- profile-interventions mapping, and dimension 4 - vigilance implementation strategy.

F2.1. Dimension 1

In this section the four domains, depicted in the excel based form, related to the Vigilance profile assessment is provided. Figure F.1 – F.4 are the four domains of the vigilance profile assessment that are found at the user interface.

Introduction **Project Information** **Next**

1. Is this project primarily focused on the capturing of ADRs¹ or are you trying to build a culture of drug safety reporting?
2. Is the project aimed at reporting of one specific drug or any drugs?
3. Is this project considering newly released² drug(s)?
4. Is the project aimed at only reporting and capturing of specific ADRs?
5. Does this project consider drugs not licensed by the regulatory authority?
This includes the following: homeopathic medicines, supplements and/or traditional medicines³?
6. Does this project require a dedicated database?
7. Is this project aimed at only targeting a specific set of healthcare provision facilities?

1. Adverse drug reactions (ADRs) are unintended or noxious responses to a drug which is taken at a normal dosage.
2. Newly released drugs refer to drugs that have till date not yet been released to the specific market.
3. Traditional medicines are skills and practices based on indigenous cultural believes and theories used to prevent, diagnose, improve or treat health related illnesses.

Figure F.1: Vigilance profile assessment: Project information

Back

Patient Information

Next

Please answer the following questions to the best of your ability

1. Is this project targeted at a well defined, controlled patient group?

2. Would it be required that your patients visit a healthcare facility or healthcare practitioner to report ADRs?

3. Will your patient have some knowledge on their specific treatment (drug), ADRs and/or the reporting process?
In other words will your patient be able to identify an ADR and report it.

4. Will the project cater for any of the following patient groups: pregnant patients, pediatrics, elderly patients and/or first regime patients?

Figure F.2: Vigilance profile assessment: Patient information

Back

Resource availability

Next

Please answer the following questions to the best of your ability

1. Is there access to a facility for the reporting of ADRs? Can this facility be used for educational and response purposes?

2. What is the availability of these resources to report ADRs?

<i>Doctors</i>	
<i>Nurses</i>	
<i>Student interns</i>	
<i>Other experts in drug safety monitoring</i>	

3. What level of experience on ADR identification and reporting would the following healthcare practitioners have?

<i>Doctors</i>	
<i>Nurses</i>	
<i>Student interns</i>	
<i>Other experts in drug safety monitoring</i>	

4. Does the project have the ability to facilitate a sole person/ department for ADR reporting and drug safety monitoring?

Figure F.3: Vigilance profile assessment: Human resource availability

Back	<h2>Technology readiness & maturity</h2>	Personalised Vigilance Implementation strategy
<p>Please answer the following questions to the best of your ability</p>		
<p>1. Is there access to cellular network at the reporting facility?</p>		
<p>2. Is there access to the internet at the reporting facility?</p>		
<p>3. Is there access to a suitable device (e.g. desktops, tablets etc.):</p>		
<p><i>For the purpose of ADRs reporting and data capturing.</i></p>		
<p><i>For the process of data analysis.</i></p>		
<p><i>For other purposes such as communication, providing feedback etc.</i></p>		
<p>4. Is there access to <i>mobile</i> devices at the facility for the purpose of ADR reporting?</p>		
<p>5. Do you have access to data processing software for ADR reporting?</p>		
<p>6. Is there room for expanding technology or conducting research and development with regards to new technologies within drug safety monitoring?</p>		
<p>7. Would your patients be likely to have access to a mobile device?</p>		
<p>8. Would your patients be likely to have access to the Internet?</p>		

Figure F.4: Vigilance profile assessment: Technology resource availability

F2.2. Dimension 2

In this section the second dimension – the Vigiance System Componet- Intervention Index is depicted in the excel based form in Figure F.5.

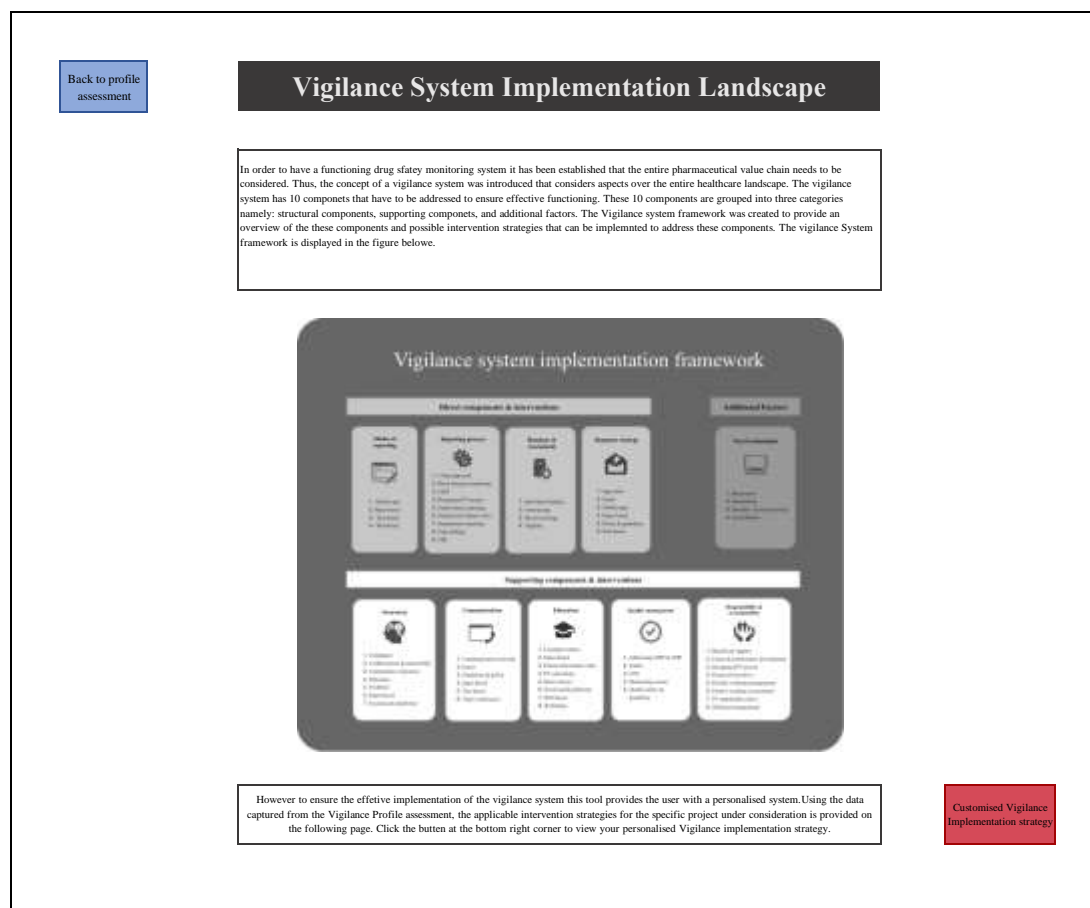


Figure F.5: Dimension 2: Vigilance System Component-Intervention Index

F2.3. Dimension 3

In this section the third dimension, the profile-intervention mapping tool in the excel based form is provided, See Figure F.6, Figure F.7, and Figure F.8.

a	Database				Mode of reporting				Reporting Process										Response strategy					
	Individual Database	Vigibase	Outsourcing	Physical storage	Text-based reporting	Mobile application reporting	web-based reporting	paper-based reporting	spontaneous reporting	CEM	TSR	Scintal surveillance sites	3-step approach	task-shifting	Patient direct reporting	Black triangle reporting	Designated PV person	Mobile applications	Email	Web-based	Paper-based	App alerts	Policy & guidelines	
Project Information																								
1. Is this project solely focused on the capturing of ADRs or are you trying to build a culture of drug safety reporting?																								
Building a culture of drug safety reporting																								
2. Is the project aimed at reporting for one specific drug or any drugs?																								
Any drug																								
3. Is this project considering "new released" drugs?																								
Yes																								
4. Is the project aimed at only reporting & capturing of specific ADRs?																								
Yes																								
5. Is this project considering "traditional medicines"?																								
No																								
6. For this project do you need a unique role database?																								
Yes																								
7. Is this project aimed at only targeting specific and limited facilities?																								
Yes																								
Viable Options for project information																								
Individual Database, Vigibase, Outsourcing, Physical storage, Text-based reporting, Mobile application reporting, web-based reporting, Paper-based reporting, Spontaneous reporting, CEM, TSR, Scintal surveillance sites, 3-step approach, task-shifting, Patient direct reporting, Black triangle reporting, Designated PV person, Mobile applications, Email, Web-based, Paper-based, App alerts, Policy & guidelines																								
Patient Information																								
1. Is this project targeted at a well defined, controlled patient group?																								
No																								
2. Would it be required that your patients visit a healthcare facility or healthcare practitioners to report ADRs?																								
Patients																								
3. Will you patient have knowledge on their specific treatment (drugs, ADRs & the reporting process)?																								
Knowledge on none																								
4. Will the project cater for any specialised patient groups such as pregnant patients, adolescents, elderly patients and/or first episode patients?																								
Yes																								
Viable Options for patient information																								
Individual Database, Vigibase, Outsourcing, Physical storage, Text-based reporting, Mobile application reporting, web-based reporting, Paper-based reporting, Spontaneous reporting, CEM, TSR, Scintal surveillance sites, 3-step approach, task-shifting, Patient direct reporting, Black triangle reporting, Designated PV person, Mobile applications, Email, Web-based, Paper-based, App alerts, Policy & guidelines																								
Resource availability																								
1. Is there access to a facility for the reporting of ADRs? Can this facility be used for educational and response purposes?																								
Access to a facility for reporting, and educational response																								
2. Who would be able to report ADRs. Which of the following HCP will be "available" at the facility?																								
3. What is the availability of these resources to report ADRs?																								
Doctors																								
Nurses																								
Student nurses																								
Other experts in drug safety monitoring																								
Does the project have the ability to facilitate a site person/ department for ADR reporting and drug safety monitoring?																								
Yes																								
Viable Options for resource availability																								
Individual Database, Vigibase, Outsourcing, Physical storage, Text-based reporting, Mobile application reporting, web-based reporting, Paper-based reporting, Spontaneous reporting, CEM, TSR, Scintal surveillance sites, 3-step approach, task-shifting, Patient direct reporting, Black triangle reporting, Designated PV person, Mobile applications, Email, Web-based, Paper-based, App alerts, Policy & guidelines																								
Technology readiness & maturity																								
1. Is there access to cellular network at your facility?																								
No																								
2. Is there access to internet at your facility?																								
Yes																								
3. Will you have access to computer/ laptop/ tablet for:																								
3.1 The purpose of capturing ADRs																								
3.2 For the purpose of data capturing & monitoring																								
3.3 For additional other purposes																								
4. Will there be access to mobile devices at the facility for the purpose of ADR reporting?																								
Yes																								
5. Do/ Will you be able to gain access to diagnostic/monitoring software for ADR reporting?																								
Yes																								
6. Is there room for expanding technology or conducting R&D with regards to new technologies within drug safety monitoring?																								
No																								
7. Does/ Will your patients have access to internet?																								
No																								
8. Does/ Will your patients have access to a mobile device?																								
No																								
Viable Options for technology readiness & maturity																								
Individual Database, Vigibase, Outsourcing, Physical storage, Text-based reporting, Mobile application reporting, web-based reporting, Paper-based reporting, Spontaneous reporting, CEM, TSR, Scintal surveillance sites, 3-step approach, task-shifting, Patient direct reporting, Black triangle reporting, Designated PV person, Mobile applications, Email, Web-based, Paper-based, App alerts, Policy & guidelines																								
Viable options after analysis																								
Individual Database, Vigibase, Outsourcing, Physical storage, Text-based reporting, Mobile application reporting, web-based reporting, Paper-based reporting, Spontaneous reporting, CEM, TSR, Scintal surveillance sites, 3-step approach, task-shifting, Patient direct reporting, Black triangle reporting, Designated PV person, Mobile applications, Email, Web-based, Paper-based, App alerts, Policy & guidelines																								

Figure F.6: Background logic related to direct components and intervention strategies

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Novel technologies			
Blockchain	Datamining	Machine learning & deep learning	Social media
Building a culture of drug safety reporting	Building a culture of drug safety reporting	Building a culture of drug safety reporting	Building a culture of drug safety reporting
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
Blockchain	Datamining	Machine learning & deep learning	Social media

NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
Blockchain	Datamining	Machine learning & deep learning	Social media

NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
NOT applicable	Not applicable	Not applicable	Not applicable
NOT applicable	Not applicable	Not applicable	Not applicable
NOT applicable	Not applicable	Not applicable	Not applicable
NOT applicable	Not applicable	Not applicable	Not applicable
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	NOT REQUIRED
Blockchain	Datamining	Machine learning & deep learning	Social media

NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	REQUIRED
REQUIRED	REQUIRED	REQUIRED	NOT REQUIRED
REQUIRED	REQUIRED	REQUIRED	REQUIRED
REQUIRED	REQUIRED	REQUIRED	REQUIRED
REQUIRED	REQUIRED	REQUIRED	REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	REQUIRED
REQUIRED	REQUIRED	REQUIRED	REQUIRED
REQUIRED	REQUIRED	REQUIRED	REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	REQUIRED
NOT REQUIRED	NOT REQUIRED	NOT REQUIRED	REQUIRED

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Figure F.8: Background logic related to additional factors and intervention strategies

F2.4. Dimension 4

In this section the customised vigilance implementation strategy is provided in the excel based form. This implementation strategy is subdivided into the categories (i) direct components (see Figure F.9) , (ii) supporting components (see Figure F. 10) and (iii) additional factors (see Figure F.11).

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Customised Vigilance Implementation Strategy

For the specific project under consideration, the following intervention strategies were identified as the most applicable to consider. However the full list of the different intervention strategies are provided if you would wish to consider these strategies.

Direct components					
The direct components refer to the components required within a PV system that directly impact the process of the reporting, managing and processing of the reported ADRs.					
Vigilance system component		Intervention strategies			Important additional information to consider
Name	Definition	Intervention strategy identified	Yes/No	Definition	
Mode of reporting	One of the minimum requirements for a PV system is that the system has a functioning reporting system which is essential for the reporting of ADRs. This requirement can be met in different possible ways that can be used to report ADRs.	Text-based reporting	No	The method is a paper-based, quick method using short messages to report ADRs. Patients receive a short message reporting of any medicines that they suspect are a problem or require a change in dose, dosage, drug interactions and so on and can be used to report any change in symptoms.	The Vigilance Monitoring system has guidelines to ensure that all ADRs are reported. ADR reports must contain the following information: Patient information (age, sex), Description of ADR, Reported patient (name, phone number, address, occupation, bank number).
		Mobile application reporting	No	The method is a paper-based, quick method using short messages to report ADRs. Patients receive a short message reporting of any medicines that they suspect are a problem or require a change in dose, dosage, drug interactions and so on and can be used to report any change in symptoms.	
		Web-based reporting	Yes	The method is a paper-based, quick method using short messages to report ADRs. Patients receive a short message reporting of any medicines that they suspect are a problem or require a change in dose, dosage, drug interactions and so on and can be used to report any change in symptoms.	Additionally include a section on specified patient (age, gender, previous history)
		Phone-based reporting	Yes	The method is a paper-based, quick method using short messages to report ADRs. Patients receive a short message reporting of any medicines that they suspect are a problem or require a change in dose, dosage, drug interactions and so on and can be used to report any change in symptoms.	
		Spontaneous reporting	Yes	Spontaneous reporting provides early rapid detection of a medication which leads to further investigation, regulatory monitoring or product changes. Spontaneous reporting is a passive form of reporting and does not require the assistance of the patient to report an ADR. Furthermore, it does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	
Reporting process	The WHO states that one of the minimum requirements for a functioning PV system is that the system has a functioning reporting system. This is one of the basic requirements for a functioning PV system to have a functioning system for the reporting of ADRs. The reporting process component refers to the possible different reporting processes that can be implemented.	CRM	No	Closed Reporting Method (CRM) is a system of PV which uses a patient who is reporting a specific medication to report the ADR. CRM involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	
		TDR	No	Targeted spontaneous reporting (TDR) involves the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	
		Statistical surveillance data	No	Statistical surveillance data involves the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	
		7-step approach	Yes	The 7-step approach involves the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	
		Task-shifting	Yes	Task-shifting involves the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	
		Patient direct reporting	No	Patient direct reporting (PDR) involves the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	
		Black triangle reporting	No	Black triangle reporting involves the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	
		Designated PV person	Yes	Designated PV person involves the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	
		Individual Database	Yes	Individual Database involves the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	
		Database & Assessment	One of the minimum requirements for a functioning PV system is that the system has a functioning reporting system. This is one of the basic requirements for a functioning PV system to have a functioning system for the reporting of ADRs. The reporting process component refers to the possible different reporting processes that can be implemented.	Vigilance	No
Openness	Yes	Openness involves the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.			
Physical storage	Yes	Physical storage involves the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.			
Response strategy	Response strategies should be implemented to ensure that the stakeholders are communicated about the report that has been received. The process to follow and the use of various strategies can be implemented to ensure that all ADRs are reported.	Feedback	No	Feedback involves the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	
		Mobile applications	No	Mobile applications involve the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	
		Local	Yes	Local involves the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	Patient does not have access to mobile device or internet. Give patient paper feedback for patient
		Web-based	Yes	Web-based involves the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	Patient does not have access to mobile device or internet. Give patient paper feedback for patient
		Phone-based	Yes	Phone-based involves the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	
Policy & guidelines	The Vigilance Monitoring system has guidelines to ensure that all ADRs are reported. ADR reports must contain the following information: Patient information (age, sex), Description of ADR, Reported patient (name, phone number, address, occupation, bank number).	App-based	No	The method is a paper-based, quick method using short messages to report ADRs. Patients receive a short message reporting of any medicines that they suspect are a problem or require a change in dose, dosage, drug interactions and so on and can be used to report any change in symptoms.	
		Policy & guidelines	Yes	Policy & guidelines involve the use of spontaneous reporting but applied more actively and within a defined setting. This involves actively following up with a patient to report an ADR. The system does not require a patient to report an ADR. It is challenging to determine the accuracy and frequency of ADRs reported.	

Figure F.9: Vigilance implementation strategy related to direct components

Supporting components						
The supporting components refer to the components and intervention strategies that assist with the effectiveness and abiding of the system.						
Vigilance system component		Intervention strategies			Important additional information to consider	
Name	Definition	Intervention strategies identified		Definition		
Awareness	Creating a culture of PV and drug safety monitoring is of the utmost importance as it will support the challenges recognized in the reporting process with regards to ADR detection, underreporting, and the quality of data. It is thus important to consider different interventions that can assist with create awareness about the importance of PV and drug safety monitoring.	Campaigns	Yes	A campaign consists of a series of planned events and activities aimed at achieving a specific objective. Campaigns that a single message and aim to convey the message to a target audience group. In 2015 the UMC initiated a campaign, Taka & Taka, with the focus of making pharmacovigilance a household word. The Taka & Taka campaign was aimed at improving the public knowledge about what PV entails through informing patients about how to report a possible side effect. The objective of the campaign was to create awareness about PV, create open communication between patients and HCP, and support active reporting of ADRs. Through the campaign a booklet IMED is provided that assists patients to monitor and report ADRs.		
		Social media platforms	No	Social media can act as a vital instrument for improving awareness on PV in the healthcare and public environments. Platforms such as YouTube, Twitter, Facebook, and LinkedIn can be used as a platform to create awareness on the importance of ADR reporting. A guideline for the specific paper can be created on these platforms that can be used to inform the public about the importance and process of reporting.		
		Paper-based	Yes	Using paper-based resources, such as pamphlets or posters, to create a culture of PV and ADR reporting can be a very effective especially in RLS. The most effective campaigns are aimed at creating awareness with the readers, and thus using tactics such as stories, images and slogans would improve the impact of the campaign. These resources can be distributed at healthcare facilities, such as clinics and hospitals, or at other public environments such as schools, libraries etc.		
		Communities of practice	Yes	Improving the awareness and PV culture within the public, focusing on patients, can be achieved through community involvement projects. This can be done through including patient members of the public into the planning phase of the project to ensure the patients' needs can be addressed. Through involving the different stakeholders in the planning phase of the project drug safety can assist with gaining knowledge on the aspects to consider when addressing communication and education interventions.		
		Collaboration & partnerships	Yes	Collaborating and partnering with existing PV bodies, healthcare facilities and pharmaceutical companies can be an effective strategy to engage with people and create awareness about PV with different stakeholders. Advancing about the importance of PV can be conducted by creating and forming partnerships with different stakeholders.		
Communication	In a PV system there are various stakeholders that play a vital role in the system. Thus, interventions are needed to create, improve, enhance and maintain communication channels between the different stakeholders. Information about ADRs received and actions taken or considering to be implemented should be communicated to the different stakeholders to ensure transparency.	Communication networks	Yes	Ensuring that there is a proper communication network plan, that indicates the flow of information between the different stakeholders is vital. The communication network plan should provide an overview of the different communication channels that have to exist between the different stakeholders. Furthermore, the communication network plan should specify the flow of information and communication tool used. This communication network needs to be designed specifically taking the project's needs into consideration.		
		Information communication technologies (ICT)		Information and Communication Technologies are technologies, primarily communication technologies such as intranet, wireless and cellular networks, that use telecommunication to provide access to information. ICT can be an effective intervention and communication tool used by different stakeholders for different reasons, from reporting, getting feedback and information then between the different stakeholders.		
		Email	Yes	As most people have access to email accounts, email communication is a very effective and commonly used. Email group can also be created to ensure the different stakeholders are kept up to date.	Patients does not have access to mobile devices or internet, thus use paper-based communication for patient	
		Text-messaging	No	Text messaging applications, like WhatsApp, are widely used in developing and developed countries for the purpose of communicating. Groups can be formed with the people of interest to ensure that the necessary information is provided to all parties a and that there is transparency when communicating about important information.	-	
		Video-conferences	Yes	Video conferencing, such as Skype, is a popular form of communicating with different parties, often when a formal meeting or discussion is required.	Patients does not have access to mobile devices or internet, thus use paper-based communication for patient	
Education	The education component addresses the different interventions that can be implemented to improve capacity building on PV and ADR reporting. The educational interventions can be targeted at the different stakeholders or audience groups and focus not only on educating on the process of reporting but also on the importance of reporting.	Paper-based	Yes	In the environments where electronic forms of communication are not a viable option, paper-based communication settings need to be in place to ensure the information flow between the different stakeholders. Printed flyers, brochures and paper-based resources can be distributed using point services.		
		Guidelines & Policies	Yes	Guidelines and policies can be used to improve communication between the different stakeholders. The guidelines should stipulate the different communication channels that have to exist between the different stakeholders. These guidelines should include a detailed description of the information flow that should exist within these communication lines.		
		Web-based	Yes	Web-based learning and PV websites can be used to improve PV education for different audience groups, from HCP, to patients. These websites can serve as a platform that can link the user to a learning resource, articles and reading materials, and assisting in webinars being held. Furthermore a website can be used as a platform to provide current news and information about pharmacovigilance and drug safety monitoring. Platforms, such as Global Pharmacovigilance (http://globalpharmacovigilance.org) have proven to be a great means for not only educational purposes but also for networking, creating awareness and providing information about current, conferences and events.		
		Learning centres	Yes	The focus of learning centres can be to create an open environment for collaboration, discussion and teaching opportunities in a more permanent basis. The learning centres can serve as an environment for PV education through providing and facilitating workshops, training courses and collaboration with other PV stakeholders. Furthermore, these learning centres can be aimed at different audience groups within the domain using and different levels of PV experience. The learning centres can host workshops aimed at students in the pharmaceutical and medical fields, conferences for experts in the field of PV or events for all audience groups.		
		PV curriculum	Yes	The WHO in collaboration with International Society of Pharmacovigilance (ISoP) and its' Education and Training Project (ETP) group developed the Pharmacovigilance Curriculum. The focus of this curriculum is to provide an overview of PV, provide information and training on new topics in PV and prepare a range of tools for practical training. The PV curriculum consist out of 13 different theoretical chapters that look at the background and history of PV, clinical aspects of ADRs, role of various ADRs, quality of data, reporting methods, regulatory bodies, conferences for experts in the field of PV or events for all audience groups.		
Quality management	In any system ensuring that proper quality management is integrated within the different system are of the utmost importance. This is true for the development of a PV system as well. The concept of quality management should not only be addressed within the process of reporting and assessing ADRs, but should also look at integration with the drug manufacturing and distribution systems.	Patient information cards	Yes	Patient information cards as a paper-based method aimed at providing the patient with information regarding their specific treatment and possible ADRs. The card contains information on the symptoms of the adverse ADRs related to the specific illness, and how and when to report the ADRs. These information cards can be paper-based or electronic, depending on the patients.	Patients information cards need to be paper-based	
		Short courses	Yes	Short courses are intensive method of education that does not require an extensive amount of time and resources that can be used to acquire, update enhance skills in PV. Short courses are aimed at teaching skills at a high level in a short amount of time. The short courses can be provided on an online platform or in a physical space such as a university or PV centres.	Patients information cards need to be prioritised as the patient has no knowledge on ADRs or the process of reporting	
		Social media platforms	No	When considering the different social media platforms and the focus of PV education, the same platforms considered would be YouTube, using video education, and Twitter and LinkedIn for creating academic networks. Currently there are a vast number of videos available on YouTube that can be used to create a culture of PV and thus it can be used to improve patient safety. There are also a lot of articles of PV knowledge in these a great resource for educating patients. When considering the networking platforms, Twitter and LinkedIn, these platforms can be used to share and distribute articles that are being published related to PV or news about situations in the PV environment.		
		Paper-based	Yes	Paper-based resources, such as pamphlets and posters, can be a very effective way of improving education on PV, ADRs and drug safety monitoring in RLS. Pamphlets and posters can be used to provide accurate and important information about what PV is, the need thereof and how to go about reporting ADRs. These paper-based educational resources can be aimed at different audience groups, however, would probably be the most effective educational resources for educating patients on PV.		
		GVP	Yes	The guidelines for GVP were published in 2010 by the EU and are divided into two main chapters: pharmacovigilance processes and population and product specific considerations. The guidelines provide an extensive overview of all the relevant aspects with regards to PV and drug safety in general. The guidelines provide best practice information about collection of the different reports, the validation and follow-up of the reports, and the data management process. Information of the use of medications during pregnancy and for paediatric and elderly also included.		
Responsibility & accountability	Responsibility and accountability are a key factor that relates to stakeholder involvement within a PV system. As there are multiple stakeholders involved within the PV system it is vital that each stakeholder understands their specific role. Responsibility refers to an individual conducting and taking ownership of a specific task, whereas accountability refers to the taking on of a liability and answerability of a task. Thus, within a system individual may be responsible for conducting a task, however the accountability lies with a different individual.	Audits	Yes	Audits play a vital role to ensure the quality standards are met and to verify any system PV system requires regular audits to be conducted. During a PV audit a number of investigations are conducted to ensure that each process meets the required quality standards. The aim is to use evidence to obtain the performance level and the effectiveness of the system. The audit also serves of the quality standards of the collection, processing and management of the data system and assessing if the database meets the current regulations. The qualification, and roles and responsibilities of the personnel are also assessed.		
		Policy & guidelines	Yes	To ensure that effective quality management is executed within the system a document plan which outlines the standard operating procedures should be developed. The document plan, policy, should ensure that the different stakeholders are clear about the different roles, responsibilities, and required task and that provision for proper control and if need be changes are included.		
		Monitoring system	Yes	Throughout the different stages and processes of the PV system quality management should be executed. The necessary authorities need to ensure that quality standards are met during the documentation, data collection, data transfer, management, validation and validation, and follow-up. Quality control procedures need to be in place to ensure that data entry and the appropriate use of terminology. Furthermore, the control data needs to be compared to the initial and follow-up data to confirm the integrity of the data. These different quality control checks need to be performed at a regular random evaluation or systematically. These monitoring system and also should take into account the pharmaceutical manufacturing companies where the drugs are manufactured.		
		Addressing GMP & GDP	Yes	As with GVP, guidelines for good manufacturing practices (GMP) and good distribution practices (GDP) have been developed by the WHO to ensure consistent quality standards are met in all aspects of drug manufacturing from material sourcing to the final product. These guidelines do also consider drug safety monitoring aspects. The WHO guidelines do include guidelines related to complaints, product recalls, quality audits, materials, and training which can be improved to incorporate PV specific aspects.		
		PV stakeholder policy	Yes	For a system to be effective it is necessary that there is a policy that stipulates a high-level statement that provides information about the overarching aim of the system. Furthermore, this policy needs to clearly define the roles, responsibilities and accountability of the different stakeholders involved. The policy needs to state the required actions called for by the stakeholders and be linked to the different standards, procedures and guidelines. Standards define the mandatory actions needed, procedures defines the operational processes to achieve the policy and guidelines provide general recommendations needed. The PV stakeholder policy refers to the development of a policy for a specific PV system that will define the roles and responsibilities of the stakeholders within that specific system. The WHO has set up a PV policy that can be used as guidelines on how to set a policy related to the stakeholder's roles for a PV system.		
Responsibility & accountability	Responsibility and accountability are a key factor that relates to stakeholder involvement within a PV system. As there are multiple stakeholders involved within the PV system it is vital that each stakeholder understands their specific role. Responsibility refers to an individual conducting and taking ownership of a specific task, whereas accountability refers to the taking on of a liability and answerability of a task. Thus, within a system individual may be responsible for conducting a task, however the accountability lies with a different individual.	Designated PV person	Yes	Having a designated member of staff that specifically takes on the role of accountability of ADR reporting within the healthcare facility would not only decrease the workload of the HCP but will also allow the concept of accountability as there would be a specific group indicated that takes on all aspects of PV. Depending on the availability of resources and the size of the healthcare facility the size of the designated PV department can be determined. The designated "main focus" as mentioned would be to report ADRs to the National PV centre and provide necessary feedback where needed. As the department would be responsible for all PV related aspects, the margin of error in the reporting process will be reduced and the process of follow-up would be easier. Furthermore, the concept of designated PV departments can also be introduced at pharmaceutical manufacturing companies to improve the relationships, communication, and responsibility of pharmaceutical manufacturing companies with the PV centres and healthcare facilities.		
		Incentive Schemes		In the healthcare facilities incentive schemes have become an emerging strategy in various fields and targeted at a range of HCP. Incentive strategies that are designed for the specific content and environment in which they will be implemented are found to be most successful. Incentives are a strategy to motivate governments and healthcare bodies to develop and sustain a desired workforce.		
		Financial incentives	Yes	There are three main financial incentives categories namely basic wages and conditions, performance-linked payments, and then additional financial services. The first category, basic wages and conditions, refers to ensuring the level of wages and satisfaction and that when compared to other colleagues. Offering a basic level of remuneration is a key element in ensuring a satisfied workforce. The second category, performance-linked payments refers to additional payments or bonuses. These forms of incentives are aimed to promote a culture of commitment of care and to ensure more experienced workforces. Bonuses paid will vary according to the duties of the individual and are linked to the individual's work performance or professional development. The last category, additional financial services, can refer to scholarships or awards for learning, transport and other expenses.		
		Career & performance development	Yes	Incentives such as access to education programs and training opportunities and experience can contribute to a supportive approach to continuous development. Through providing educational and development opportunities individuals improve their professional development which enhances their ability to financial and other benefits.		
		Workload management	No	In the healthcare facilities heavy workloads are a major concern that contributes to low motivation, poor performance or ultimately leaving the healthcare profession. Many of these factors that contribute to heavy workloads are the shortage of workers, misallocated staff, or even just an increased demand. However, there are possible methods that can be implemented to address heavy workloads. Firstly, incorporating overtime payments for staff as a compensation for working overtime and a motivation for employees to improve workload management. Secondly introducing additional hours or time-lapse to attend to care. Another possible method is to create rotating roles and responsibilities to improve workload distribution among the different staff members. Finally, the number of continuous working hours worked by staff members should be explained to more patient safety.		
Responsibility & accountability	Responsibility and accountability are a key factor that relates to stakeholder involvement within a PV system. As there are multiple stakeholders involved within the PV system it is vital that each stakeholder understands their specific role. Responsibility refers to an individual conducting and taking ownership of a specific task, whereas accountability refers to the taking on of a liability and answerability of a task. Thus, within a system individual may be responsible for conducting a task, however the accountability lies with a different individual.	Positive working environments	Yes	Ensuring a positive working environment through creating a positive organizational culture and safe working environment are critical factors for retaining staff members and improving PV outcomes. Factors to consider incorporating are decentralised organizational structures, flexible working hours, and systematic communication between management and staff. Incorporating these factors enhance the working environment by improving mood of staff members.		
		Benefits & support	Yes	Although financial incentives are not always a possibility there are other support incentives that can be utilized and provided. Such as providing housing, transport and food. Also providing centres for children or employee support.		

Figure F.10: Vigilance implementation strategy related to supporting components

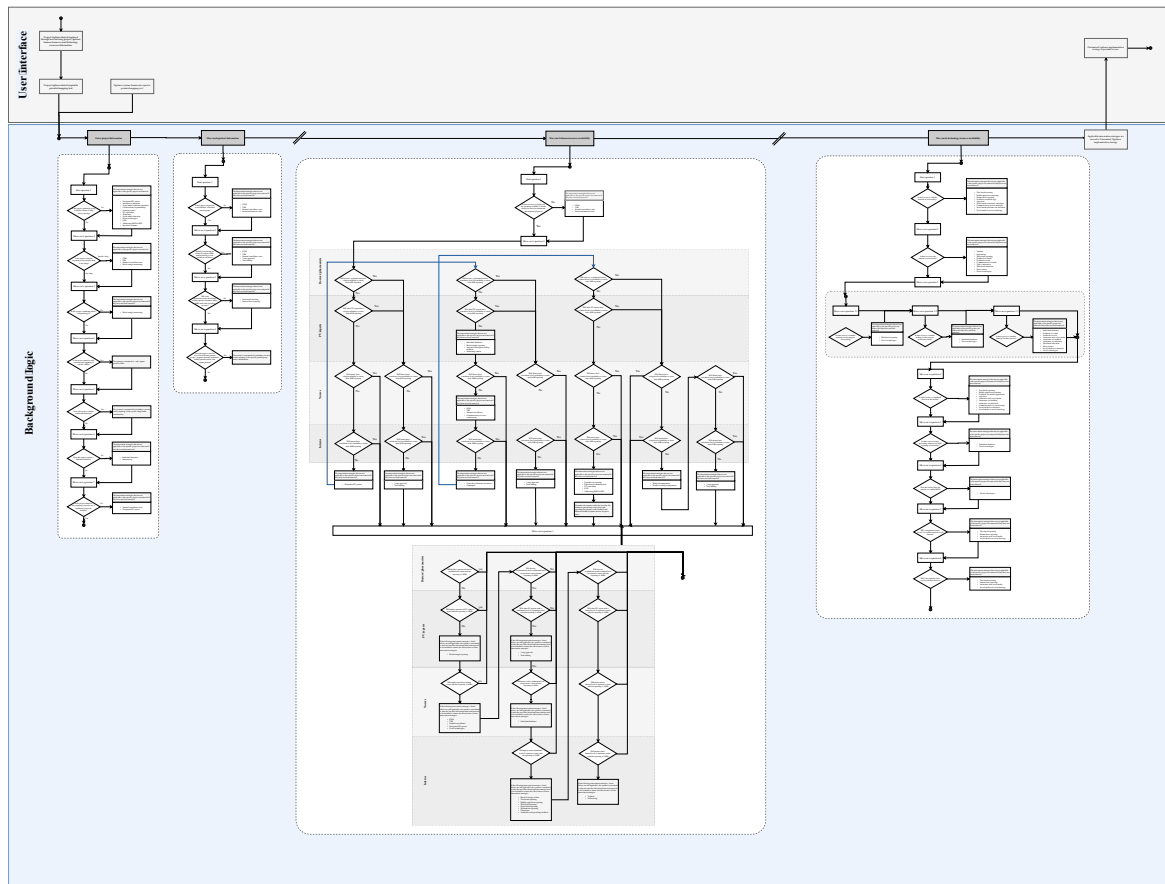
Additional factors					
Additional factors do not directly impact the reporting process, neither does it support the effectiveness of the system, but it rather provides the system with an agile component that focuses on the future of PV systems.					
Vigilance system component		Intervention strategies			Important additional information to consider
Name	Definition	Intervention strategies identified		Definition	
Novel Technologies	In the modern-day landscape with the approach of a 4th industrial revolution, everyday systems and operations. Thus, for the PV system to stay agile, continuous and incremental - novel technologies should be investigated and incorporated.	Blockchain	No	Blockchain is a form of distributing data allowing users to process data through nodes on a network instead of through a central authority. Blockchain can be a valuable asset when storing data in the digital or analogized. Blockchain also provides security. Trust of data between the different stakeholders, allowing patients direct information on the reported ADRs. Blockchain can also assist with aligning international standards of drug safety monitoring due to its distributed nature allowing a more systematic approach to data management.	-
		Data mining	No	Due to the growing development of large electronic health data storage systems and advances in technology the demand for data mining within the healthcare environment has significantly increased. Data mining, for the purpose of this study, will refer to the utilization of statistical techniques within the knowledge discovery process, which refers to the extraction process of valid, previously unknown information from large databases. Using data mining techniques data related to ADRs can be identified from massive medical databases that can be used to build a big data platform. Thus using the platform and different intelligent data processing techniques an ADR monitoring and filtering model can be built up to thus respond ADRs. The system will still require experts to confirm and check the identified suspected ADRs.	-
		Machine learning & deep learning	No	Machine learning is an application that offers a system the ability to automatically discover and learn from its past experiences to improve without being explicitly programmed. Conventional machine learning methods have been used to for gene marketing drug side effects, however the complex biological and chemical structures of drugs often make it more difficult to be detected than deep learning methods as they performed for prediction tasks. In a study done by Chen Yun Lu et al. in 2019, a two-stage framework was developed based on using deep learning methods to model the association between ADRs and drugs and integrating individual's biological data into a system. This framework can be used to determine the likelihood of an ADR occurring in a patient before a new medication is prescribed [70]. There are countless opportunities to utilize these machine learning techniques to pharmacovigilance.	-
		Social media	No	Social media generates large volumes of data that can be utilized for signal and ADR detection, advancing PV systems. The use of social media thus as platforms to facilitate discussion of ADRs between patients and HCPs have become increasingly predominant and reported ADRs from social media should also be recorded for data gathering. There are however still challenges, technical and ethical, that have to be addressed for this to become a viable intervention. Algorithms still need to be adapted to recognize language technology, identifying ADRs through posting with certainty, and intelligence regulations still have to be put in place. However, the use of social media brings with it the opportunity for early detection and subsequent of patient safety.	-

Figure F.11: Vigilance implementation strategy related to additional factor

F.3. Detailed level map for CVSIT

Figure 54 is a detailed representation of how the data gathered during the profile vigilance assessment is mapped against the criteria of a Vigilance System implementation landscape and how each of the different intervention strategies are analysed to determine if it is applicable to the specific project under consideration. In order to gain a better view of the Figure it has been subdivide into three sections, Figure F.12 – Figure F.15.

Figure F.12: Detailed level process map of CVSIT



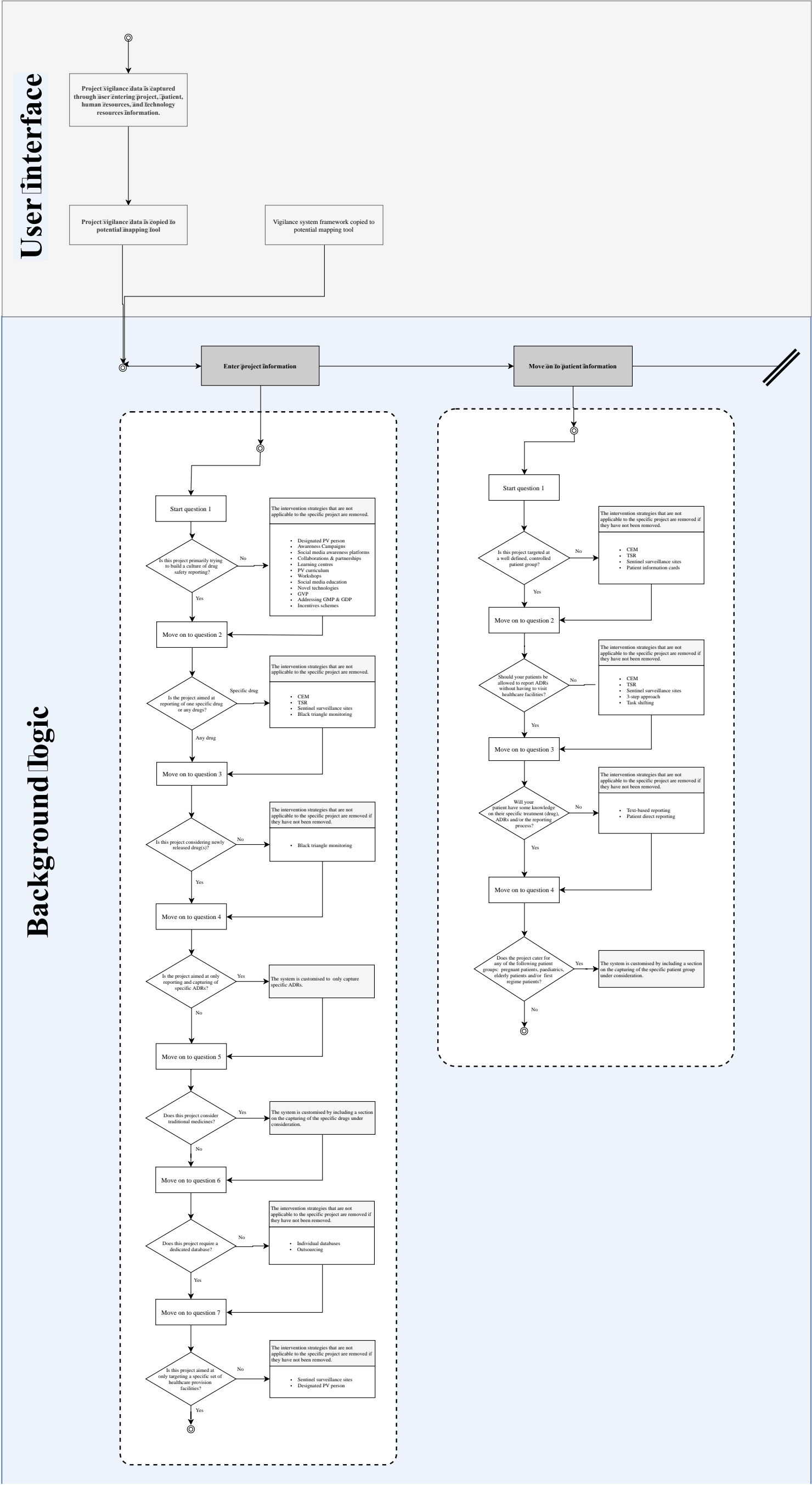
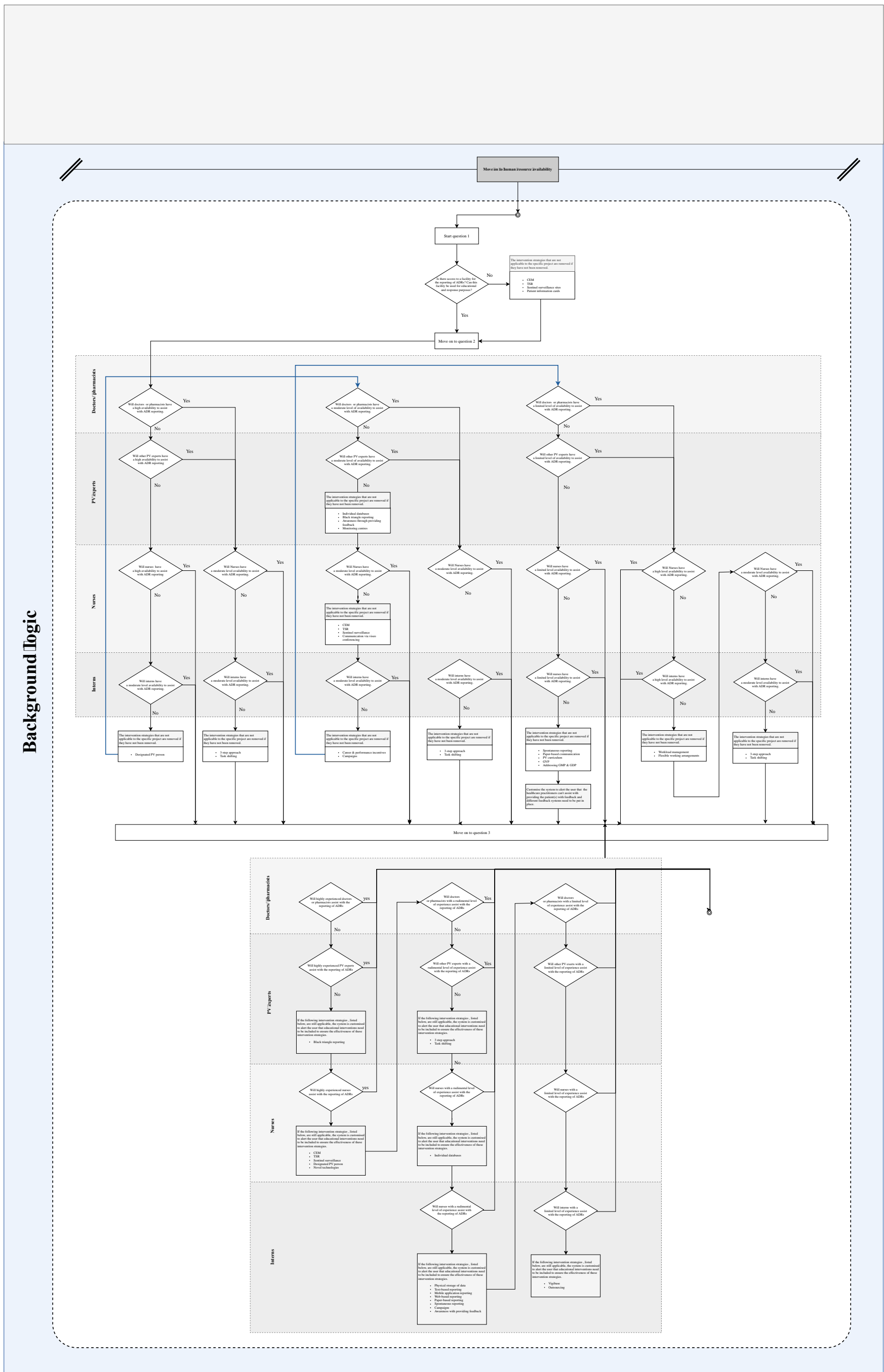


Figure F.13: Detailed level process map of CVSIT - section1



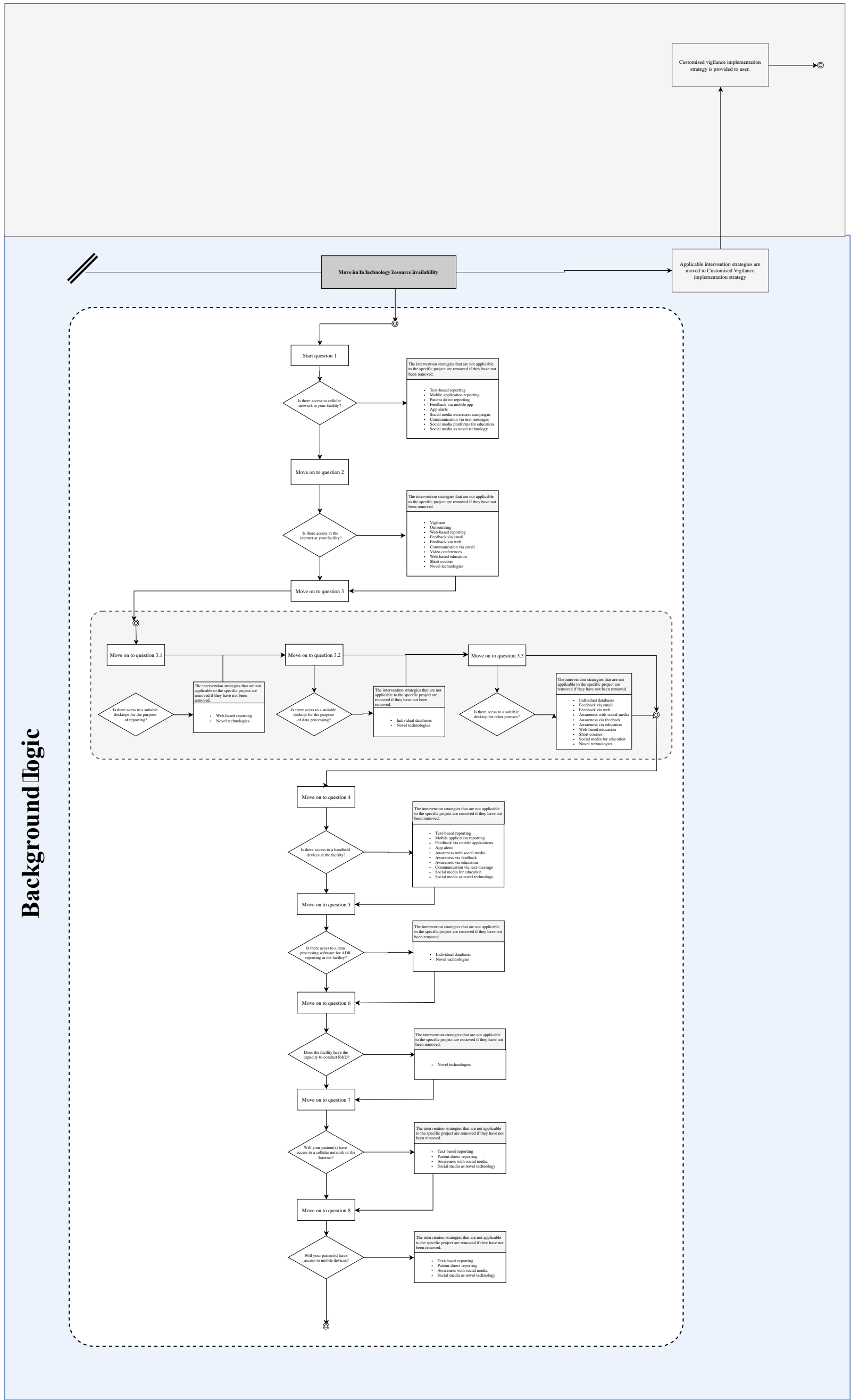


Figure F.15: Detailed level process map of CVSIT - section 3

Appendix G. Additional documents related to Case A

Appendix G provides additional information regarding the application of Case A.

The following sections are included:

G1: Information related to Vigilance profiles assessment

G2: Customised vigilance implementation strategy for Case A

G.1. Information related to Vigilance profiles assessment

In this section the resources used to complete the vigilance profile assessment for Case A is provided in Table G.1.

Table G.1: Vigilance profile assessment data for Case A

Case A		
Vigilance profile assessment domains	Explanation	References used
Project information	Information related to the specific drug being considered, the required databases and the targeted facilities	(Conradie <i>et al.</i> , 2014) (Clayden, 2014)..
Patient information	Information related to target audience group, consideration of specialised patients and PV related knowledge of patients	(Clayden, 2014; Ndjeka <i>et al.</i> , 2015)
Human resources availability	Information related to resources, HCP, availability and PV experiences	(TBFacts, no date; HR Pulse News Desk, 2019; Tshehle, 2019)
Technology resources availability	Information related to technology resources availability	(TBFacts, no date; HR Pulse News Desk, 2019; Tshehle, 2019)(South African Government, 2013)

G.2. Case A Customised vigilance implementation strategy

The customised implementation strategy for a Vigilance System for Case A is depicted in Figure G.2.

Direct components				
The direct components refer to the components required within a PV system that directly impact the process of the reporting, managing and processing of the reported ADRs.				
Vigilance system component		Intervention strategies		Important additional information to consider
Name	Definition	Intervention strategy identified	Should Intervention strategy be implemented	
Made of reporting		Free-based reporting	No	The Vigilance Monitoring units has guidelines on how to set-up an ADR reporting form.
	One of the minimum requirements for a PV system, as stated by the WHO, is that the system have a functioning reporting system with a national ADR reporting form. This component refers to the different possible methods that can be used to report ADRs.	Mobile application reporting	No	ADR reports must contain the following information: - Patient information (e.g. sex, age) - Description of ADR - Expected product information (brand name, active ingredient, batch number)
		web-based reporting	Yes	Electronic ADR reporting forms or online platform that submit ADRs on-line, convenient and made of reporting in developing and developed countries. Using online platform is efficient and cost-effective modes of reporting, that does not require an expensive amount of resources.
		paper-based reporting	Yes	The main requires the patient or HCP to complete a hard copy form and send it to the corresponding authority in post or facsimile. The paper-based reports are the simplest form and are fairly easy to develop and complete.
		spontaneous reporting	Yes	Spontaneous reporting provides early signal detection of a medication which leads to further investigation, regulatory warnings or product changes to be made. Spontaneous reporting is a positive form of reporting and then relies on the initiative of the patient to report an ADR. Furthermore, as this is a spontaneous patient follow-up, clear protocols or PV activities, it is challenging to increase the accuracy rates and frequency of ADRs reported.
Reporting process		CEM	Yes	The resources required training education on ADR identification and reporting before this intervention can be implemented
	The WHO states that one of the minimum requirements for a functional PV system is to have a functioning national reporting system. Thus, one of the basic fundamentals for a working PV system is to have an effective system for the reporting of ADRs. The reporting process component refers to the possible different reporting process that can be implemented.	TSR	Yes	The resources required training education on ADR identification and reporting before this intervention can be implemented
		Sentinel surveillance sites	No	
		3-step approach		
		task-shifting		
Database & Assessment		Patient direct reporting	No	
	One of the fundamental prerequisites for a functioning PV system is to have a national database for the collating and managing of the ADR reports.	Black sample reporting	Yes	
		Designated PV person	No	
		Individual Database	No	
		Vigibase	Yes	
Outsourcing	No			
Physical storage	Yes			
Response strategy		Feedback	No	
	Response strategies should be implemented to ensure that the stakeholders are consistent and clear the report that have received, the process to follow and in the case of serious cases that cause concern intervention that will follow to improve patient safety	Mobile applications	No	
		Email	Yes	Patient does not have access to mobile device or internet, they provide paper feedback for patient
		Web-based	Yes	Patient does not have access to mobile device or internet, they provide paper feedback for patient
		Paper-based	Yes	
App alerts	No			
Policy & guidelines	Yes			

Additional factors				
Additional factors do not directly impact the reporting process, neither does it support the effectiveness of the system, but it rather provides the system with an agile component that focuses on the future of PV systems.				
Vigilance system component		Intervention strategies		Important additional information to consider
Name	Definition	Intervention strategies identified	Definition	
New Technology	In the modern-day landscape with the approach of 4th industrial revolution, artificial intelligence (AI) is becoming part of everyday systems and operations. This, for the PV system as a way of life, computing and personal, would be technology that should be investigated and incorporated.	Blockchain	No	Blockchain is a form of distributing data allowing users to prevent data through nodes on a network instead of through a central authority. Blockchain can be a valuable asset when ensuring data is not falsified or manipulated. Blockchain also provides additional flow of data between the different stakeholders, allowing patients direct information on the reported ADRs. Blockchain can also assist with aligning international standards of drug safety monitoring due to its distributed nature allowing more systematic approach to data management.
		Datatrusting	No	One of the growing development of large electronic health data storage systems and advances in technology is the demand for datatrusting within the healthcare environment has significantly increased. Datatrusting, for the purpose of this study, will refer to the collection of medical techniques (either the knowledge discovery process, which refers to the extraction process of valid, previously unknown information from large databases. Using datatrusting techniques data related to ADRs can be identified from massive medical databases that are used to build the drug data platform. Thus using the platform and different intelligent data processing techniques as ADR monitoring and filtering model can be built up to flag suspected ADRs. The system will still require experts to confirm and check the identified suspected ADRs.
		Machine learning & deep learning	No	Machine learning is an application that offers a system the ability to automatically detect and learn from its past experience to improve without being explicitly programmed. Conventional machine learning methods have been used for the past involving drug utilization, however the complex biological and chemical structures of drugs often make it more difficult to be detected and thus deep learning methods are often preferred for product safety. In a study done by Chen Yuxian et al. in 2019, a new drug framework was developed based on using deep learning methods to predict the association between ADRs and drugs by integrating individual's biological data into a system. This framework can be used to determine the likelihood of an ADR occurring in a patient before a new medication is prescribed (75). There are various opportunities to refine these machine learning techniques to pharmaceuticals.
		Social media	No	Social media systems large volume of data that can be utilized for signal and ADR detection, allowing PV systems. The use of social media sites as platforms for detection methods of ADRs through patient and HCP data sources has been investigated and reported ADRs that social media should also be included for data gathering. There are however still challenges, cultural and ethical, that have to be addressed for the system to be viable in the community. Significant effort will have to be aligned to manage regulatory technology, handling the through patient data, consent, and non-response regulations will have to be put in place. However, the use of social media brings the opportunity for early detection and observation of patient safety.

Supporting components				
The supporting components refer to the components and intervention strategies that assist with the effectiveness and abiding of the system.				
Vigilance system component		Intervention strategies		Important additional information to consider
Name	Definition	Intervention strategies (continued)	Definition	
Awareness	Creating a culture of PV and drug safety monitoring is of the utmost importance as it will improve the challenges encountered in the reporting process with regards to ADR detection, understanding, and the quality of data. It is thus important to consider interventions that can assist with count measures that have the importance of PV and drug safety monitoring.	Campaigns	No	A campaign consists out of a series of planned events and activities aimed at achieving a specific objective. Campaigns that are single messages and aim to convey the message to a target audience group. In 2015 the CHMP initiated a campaign, 'Take it Safe, with the focus of raising pharmacovigilance awareness. The Table 4.7-10: Campaign was aimed at increasing the public knowledge about what to watch during information patients about how to report a possible side-effect. The objective of the campaign was to create awareness about PV, create open communication between patients and HCP, and support active reporting of ADRs. Through the campaign, a media kit was provided that contains patient report ADRs.
		Social media platforms	No	Social media sites should be a vital instrument for improving awareness on PV in the healthcare and pharmaceutical industries. Platforms such as YouTube, Twitter, Facebook, and LinkedIn can be used as a platform to create awareness in the reporting of ADR reporting. A profile for the specific purpose can be created on these platforms that can be used to inform the public about the importance and process of reporting.
		Paper-based	Yes	Using paper-based resources, such as posters or pamphlets, to create a culture of PV and ADR reporting can be a very effective especially in RLS. These materials are aimed at providing resources to the individuals, and distributed throughout the premises where the patient needs to be informed. It improves the impact of the campaign. These resources can be distributed at healthcare facilities, such as clinics or hospitals, or at other public environments such as schools, libraries, etc.
		Commitment of practice	Yes	Improving the awareness and PV culture within the public, focusing on patients, can be achieved through community involvement projects. This can be done through involving patients' members of the public into the planning phase of the project to ensure the patient's needs are addressed. Through involving the different stakeholders to the planning phase of the project's drug safety can assist with gaining knowledge on the aspects to consider when addressing communication and education measures.
		Collaborations & partnerships	No	Collaborating and partnering with existing PV bodies, healthcare facilities and pharmaceutical companies can be an effective strategy to improve the impact of the intervention with the different stakeholders. Advancing these interventions of HCPs can be achieved by creating and building partnerships with different stakeholders.
		Providing Feedback	No	Providing feedback on the monitoring of reports are important, however to create a culture of PV, more detailed feedback should be provided to the patient. This should include a return of the report to the patient, and a feedback letter from the healthcare facility. The patient's report should be reviewed. The feedback system should also consider providing some form of a "closing" system of the report, to help the patient up to date, if not used with to last state.
		Education	No	Education of PV can improve the culture of reporting through ongoing training.
		Communication networks	Yes	Ensuring that there is proper communication network place, that indicates the flow of information between the different stakeholders in the healthcare system. The communication network place should provide an overview of the different communication channels that have to exist between the different stakeholders. Furthermore, the communication network place should specify the flow of information and communication tool used. This communication network can be designed specifically, using the project's work flow considerations.
		Information communication technologies (ICT)	Information and Communication Technologies are technologies primarily communication technologies such as internet, wireless, and other networks, that are telecommunicative to provide access to information. ICT can be an effective intervention and communication tool used by different stakeholders to improve their services, thus reporting, providing feedback and information flow between the different stakeholders.	
		Communication	Is a PV system there are various stakeholders that play a vital role in the system. Thus, interventions are needed to create, improve, enhance and maintain communication channels between the different stakeholders. Information about ADRs received and action taken are considered to be implemented should be communicated to the different stakeholders to ensure transparency.	Is not
Is not	No			As most people have access to smart devices, smart communication is a very effective and convenient tool. Email groups can also be created between the different stakeholders to ensure transparency.
Is not	Yes			Video conferencing, such as Skype, is a preferred form of communicating with different groups, thus when a virtual meeting is deemed to be required.
Is not	Yes			In the environments where electronic forms of communication are not a viable option, paper-based communication settings need to be in place to ensure the information flow between the different stakeholders. Formal letters, worded paper-based notices can be distributed using postal services.
Is not	Yes			Guidelines and policies can be used to improve communication between the different stakeholders. The guidelines should stipulate the different communication that should exist within these communication flows.
Is not	Yes			With-hand learning and PV education can be used to improve PV education for different audience groups, from HCPs to patients. These activities can serve as a platform that can link the two to a learning resource, written and/or verbal materials, and training in working with hand. Furthermore a culture of PV can be used as a platform to provide count rates and information about pharmacovigilance and drug safety monitoring. Written, such as Global Pharmacovigilance (global-pharmacovigilance.org) may prove to be a great resource for any individual projects due to its accessibility, creating resources and providing information about issues, confidence and costs.
Is not	No			The focus of learning centers are to create an open environment for collaboration, discussion and learning opportunities in a more personal basis, thus learning centers are used to increase on PV education through providing and facilitating workshops, training courses and other activities with other PV bodies. Furthermore, these learning centers can be aimed at different target audience groups within the healthcare system and different levels of PV expertise. The training centers can have workshops aimed at matters in the pharmaceutical and medical fields, conferences to report in the field of PV or across for all audience groups.
Is not	No			The WHO to collaborate with International League of Pharmacologists (ILIP) and 'E' Education and Training Project (ETP) group developed the WHO PV course materials. The WHO course materials are available in a number of languages and can be used to improve PV education. The WHO PV course is a range of value for practical training. The PV curriculum consists of 10 modules that cover the following topics: the role of PV, the objectives

Figure G.2: Case A customised vigilance implementation strategy

Appendix H. Additional documents related to Case B

Appendix H provides additional information regarding the application of Case B.

The following sections are included:

H1: Information related to Vigilance profiles assessment

H2: Customised vigilance implementation strategy for Case B

H.1. Information related to Vigilance profiles assessment

In this section the resources used to complete the vigilance profile assessment for Case B is provided in Table H.1.

Table H.1: Vigilance profile assessment data related to Case B

Case B		
Vigilance profile assessment domains	Explanation	References used
Project information	Information related to the specific drug being considered, the required databases and the targeted facilities	(Global TB Community Advisory Board, 2018), (SAnews, 2018)
Patient information	Information related to target audience group, consideration of specialised patients and PV related knowledge of patients	(Clayden, 2014; Ndjeka <i>et al.</i> , 2015; Global TB Community Advisory Board, 2018; SAnews, 2018)
Human resources availability	Information related to resources, HCP, availability and PV experiences	(TBFacts, no date; Mathlathi <i>et al.</i> , 2015; HR Pulse News Desk, 2019; Tshehle, 2019)
Technology resources availability	Information related to technology resources availability	(TBFacts, no date; Mathlathi <i>et al.</i> , 2015; HR Pulse News Desk, 2019; Tshehle, 2019)

H.2. Case B Customised vigilance implementation strategy

The customised implementation strategy for a Vigilance System for Case B is depicted in Figure H.1.

Direct components						
The direct components refer to the components required within a PV system that directly impact the process of the reporting, managing and processing of the reported ADRs.						
Vigilance system component		Intervention strategies			Important additional information to consider	
Name	Definition	Intervention strategies identified	Should intervention strategy be implemented	Definition		
Main of reporting	One of the minimum requirements for a PV system, as stated by the WHO, is that the system has a functioning reporting system with a national ADR reporting form. This component refers to the different possible methods that can be used to report ADRs.	Year-based reporting	No	This method is a paperless, quick method using text messages to report ADRs. Patients receive a text message prompting if any reactions have been noticed and are asked to reply to using a text message. Simple technologies such as Facebook can be used to create a text message database.	The Uptake Monitoring centre has guidelines on how to set up an ADR reporting form.	
		Mobile application reporting	No	This method is a paperless, quick and simple way of reporting and managing ADRs reports. An app can be created that uses simple techniques to prompt the user to enter information (reporter information and information on the reported adverse event) and once the data is captured it goes into the required monitoring centre.	ADR reports need to contain the following information: (1) Patient information (e.g., sex) (2) Description of ADR (3) Suspected product information (brand name, active ingredients, batch number)	
		Web-based reporting	Yes	Electronic ADR reporting forms or online platforms used to submit ADRs are most commonly used mode of reporting to developing and developed countries. Using an online platform is efficient and cost-effective mode of reporting, that does not require an extensive amount of resources.		
		paper-based reporting	Yes	The study requires the patient or HCP to complete a hard copy form and send it to the corresponding authority via post or facsimile. The paper-based reports are the simplest form and are fairly easy to develop and complete.		
Reporting process	The WHO states that one of the minimum requirements for a functional PV system is to have a functioning national reporting system. Thus, one of the basic fundamentals for a functional PV system is to have a functional system for the reporting of ADRs. The reporting process component refers to the possible different reporting process that can be implemented.	spontaneous reporting	Yes	Spontaneous reporting provides early signal detection of a medication which leads to further investigation, regulatory warnings or product changes to be made. Spontaneous reporting is a passive form of reporting and thus relies on the initiative of the patient to report an ADR. Furthermore, as there is no systematic patient follow-up, clear process or PV number, it is challenging to document the accurate rate and frequency of ADRs reported.		
		CEM	Yes	Global Event Monitoring (CEM) is an active form of PV which need to monitor ADRs in patients who are receiving a specific treatment regimen in a hospital or acute care facility. CEM involves actively following up with a cohort of patients to register all ADRs that occur during and for a short period after the patient's treatment. CEM also covers all other medicines-related events, from medication errors, issues brought on by past therapy, medication use, drug quality, medication storage, drug interactions and adverse events resulting from the use of the drug. The PV method is particularly applicable during the early stages of exposure to a new medicine in the field as it is systematic, and completely method of monitoring.	The resources required training/ education on ADR identification and reporting before this intervention can be implemented.	
		TSR	Yes	Targeted spontaneous reporting (TSR) builds on the principles of spontaneous reporting but applied more actively and within a defined setting. This method requires HCP to manage a well-defined patient group and report specific medicine-related safety concerns. TSR can be considered to offer report all reported ADRs experienced by the group or focus on specific reactions that are of particular concern, in order to limit the ADRs to those who are at most at risk of exposure. This method is a particularly significant method to use for targeted follow-up of patients.	The resources required training/ education on ADR identification and reporting before this intervention can be implemented.	
		structured surveillance sites	No	structured surveillance operates by selecting specific reporting units that have a higher probability with addressing cases after the three under consideration and have been highly qualified and experienced staff. Structured surveillance only involves a limited, specific network. Sites method and supervisor can be provided, in several sites are located in those facilities which report more to higher quality data being obtained.		
		3-step approach	Yes	This approach looks at utilizing different subcategories for the different phases of the reporting process. The first step refers to using any available data from the qualification method to generate the data by filling out a clinical trial. The second step involves a clinical trial with ADRs as a phenomenon or event, to collect the data from the various treatment centres and the third step is to then select the data to the necessary control step, such as the National PV centre or WHO.		
		task-shifting	Yes	This process entails having tasks such as completing ADR reports and collecting data to be 'task-shifted' to HCP with a limited level PV knowledge but to ensure or monitor outcomes.		
		Patient direct reporting	No	Remote direct reporting (DRM) entails having the patients directly report the reported ADRs to the National PV centres. To date the most common form of DRM is through using mobile applications, such as the UK's Yellow Card Scheme which is a paper-based scheme that has been adapted to online platform, that are directly linked to the database.		
		Black triangle reporting	Yes	Black triangle monitoring was introduced for medicines that are under additional monitoring, and being monitored more closely by regulatory authorities. The reason for the more intensive monitoring is because there is generally less safety information available on that medicine, a certain new active substance, the medicine has only been approved under exceptional circumstances, it is a 'biological medicine' or the manufacturing process is required to perform additional monitoring for example based on a rare side effect that was identified during the clinical trial phase. Drugs under black triangle monitoring are denoted with a black inverted triangle (∇) rather than a three vertical reporting the meaning of it.		
		Dedicated PV person	No	This initiative is aimed at introducing a dedicated department in the reporting and other PV related processes. A dedicated PV person department is only implemented in the healthcare facilities that have the responsibility of monitoring all PV related areas. Once reporting of ADRs in the country, healthcare and follow-up with patients. This department can also be more actively involved in providing PV education.		
		Individual Database	No	A database can be created to capture this project specific ADR data and information. The database developed should be classified, easily stored and managed, secure and have some degree of confidentiality. The WHO and UK's CEM provide guidelines on how to set up an unclassified data and information that can be maintained in specific range.		
Database & Assessment	One of the fundamental properties for a functioning PV system is to have a national database for the collecting and managing of the ADR reports.	Vigibase	Yes	Vigibase (https://www.who.int/teams/vigilance/vigibase) is a database system used for data management and processing which is reported by the WHO as a tool of the WHO. The main use of Vigibase is to collect and analyse the ADR reports of all members of the WHO Drug Monitoring program.		
		Outsourcing	No	There is a variety between the Private Vigilance or Outlets, that maintain global adverse drug reporting databases. These companies provide services for the processing, monitoring and reporting of ADRs and enable clients to view their data in real time.		
		Physical storage	Yes	For the case of paper-based reporting the reporting forms need to be stored in a safe space once they have been updated to the specific database, as the reports need to be maintained for a certain period of time. The reports need to be organized in a such a manner that the information is completely understood, i.e. listing or describing the documents.		
Response strategy	Response strategies should be implemented to ensure that the stakeholders are communicated about the report that has been received, the process to follow and in the case of severe dangerous cases the intervention that will follow to improve patient safety.	Feedback	No	In any reporting system it is essential that the participants receive feedback. The feedback should include providing confirmation of that the report has been received and in it needed the necessary actions to be taken. In a PV system it is crucial that the response is provided with feedback, as the reporting of ADRs has been received with a feedback. The content and the mode in which the feedback is given, the method, is a combination of ensuring the ADR report is reported, however a study done with regards to drug discovery found that other patients have been found for more information regarding their reported ADR [26]. For example, patients would like to be informed if the report has contributed, if more reports were received and if necessary, action has been taken.		
		Mobile application	No	Mobile applications can be created with the purpose of reporting and providing the reported with feedback. The mobile application can also provide additional information on the report and what to do next.		
		Email	Yes	An email response and feedback system can be created to immediately inform the reporter about receiving the report. The email can also provide additional information to the reporter about the process that will follow after the report has been received and actions that might be taken.	Patient does not have access to mobile devices or internet, then provide paper-based for patient	
		Web-based	Yes	Web-based platforms, such as Vigibase (https://www.vigibase.org), which allows members of the public, information about the amount of reports received and the level of ADR reported for every drug.	Patient does not have access to mobile devices or internet, then provide paper-based for patient	
		Paper-based	Yes	Paper-based resources, such as formal letters or newsletters, can be distributed using postal services to the different reporters. Newsletters that provide information about the reported ADRs, can also be distributed to healthcare facilities.		
		App alerts	No	This intervention is aimed at informing HCP, pharmacist and doctors about drugs that are reported to cause serious drug reactions or be of sub-standard quality. The focus of the alert is only to inform HCP if immediate action needs to be taken. The app alerts should work on a security scale, as app provides alert of a drug, but not a high volume of reports in a specific time frame.		
		Policy & guidelines	Yes	Education need to be created to ensure that there is an effective, achievable response strategy in place for when a report drug has been identified and made to further monitoring or further action needs to be taken such as monitoring the drug from the market. The guidelines need to be clear about the steps app alerts need to be taken by each of the stakeholders during the response strategy. These guidelines should require the actions that pharmaceutical manufacturing companies need to take when a drug needs to be monitored more carefully or be taken off the market.		

Additional factors						
Additional factors do not directly impact the reporting process, neither does it support the effectiveness of the system, but it rather provides the system with an agile component that focuses on the future of PV systems.						
Vigilance system component		Intervention strategies			Important additional information to consider	
Name	Definition	Intervention strategies identified		Definition		
New Technologies	In the modern-day landscape with the approach of a 4th industrial revolution, artificial intelligence (AI) is becoming part of everyday system and operations. Thus, for the PV systems to stay agile, continuous and permanent - novel technologies should be developed and incorporated.	Blockchain	No	Blockchain is a form of distributing data allowing users to process data through nodes on a network instead of through a central authority. Blockchain can be a valuable source when storing data as not falsified or manipulated. Blockchain data provides reliable flow of data between the different stakeholders, allowing patients direct information on the reported ADRs. Blockchain can also assist with aligning international standards of its, any possible interfering data or a distributed nature allowing a secure transparent, open and non-manipulated.		
		Data mining	No	Due to the growing development of large electronic health data storage systems and advances in technology, the demand for data mining within the different environments has significantly increased. Data mining, the process of analysing the data, will allow the predictive of medical outcomes within the knowledge discovery process, which refers to the extraction process of valid, previously unknown information from large databases. Mining techniques require data related to ADRs to be collected from various medical facilities that can be used to build the data platform. Thus using this platform and different intelligent data processing techniques at ADR monitoring and filtering could be built up to filter reported ADRs. The system will still report reports to confirm and make the identified reported ADRs.		
		Machine learning & deep learning	No	Machine learning is an application that offers a system the ability to automatically detect and learn from its past experiences to improve without being explicitly programmed. Conventional machine learning methods have been used in the past predicting drug side effects, however the complex biological and chemical structures of drugs often make it more difficult to be detected and thus deep learning methods are often preferred for this purpose. It is a study done by Chen, Liu, et al. (2015), a new deep framework was developed based on using deep learning methods to predict the association between ADRs and drugs and integrating individual's biological data into a system. This framework can be used to determine the likelihood of an ADR occurring in a patient before a new medication is prescribed [27]. Thus an exciting opportunity to utilize these machine learning techniques in pharmacovigilance.		
		Social media	No	Social media generates large volumes of data that can be utilized for signal and ADR detection, enhancing PV systems. The use of social media platforms to facilitate discussions of ADRs between patients and HCPs have become increasingly predominant and reported ADRs from social media should also be considered for drug gathering. There are however still challenges related and ethical, due to the need to address the data to become a viable intervention. Algorithms need to be adjusted to interpret linguistic technology, identifying ADRs through parsing with sentiment, and monitoring negative off-line to be the top of the page. However, the use of social media brings with it the opportunity to only detection and enhancement of patient safety.		

Supporting components

The supporting components refer to the components and intervention strategies that assist with the effectiveness and abiding of the system.					
Vigilance system component		Intervention strategies		Important additional information to consider	
Name	Definition	Intervention strategies identified	Definition		
Awareness	Creating a culture of PV and drug safety monitoring is of the utmost importance as it will improve the challenges recognised in the reporting process with regards to ADR detection, understanding, and the quality of data. It is thus important to consider interventions that can assist with creating awareness about the importance of PV and drug safety monitoring.	Campaigns	No	A campaign consists of a series of planned events and activities aimed at achieving a specific objective. Campaigns share a single message and aim to convey the message to a target audience group. In 2015 the DME national campaign, Table A TdL with the focus of raising pharmacovigilance a household word. The Table A TdL campaign was aimed at improving the public knowledge about what PV entails through educating patients about how to report a possible side-effect. The objectives of the campaign are to create awareness about PV, create open communication between patient and DCP, and support active reporting of ADRs. Through the campaign a toolkit M202 is provided that assists patients to monitor and report ADRs.	
		Social media platforms	No	Social media can thus be a vital instrument for improving awareness on PV in the healthcare and public environments. Platforms such as WhatsApp, Twitter, Facebook, and LinkedIn can be used as a platform to create awareness on the importance of ADR reporting. A guideline for the specific platform can be created as these platforms can be used to inform the public about the importance and process of reporting.	
		Poster-based	Yes	Using poster-based resources, such as posters or pamphlets, to create a culture of PV and ADR reporting can be very effective especially in BSA. The most effective campaigns are aimed at creating awareness with the markers, and then using tactics such as stories, images and slogans would improve the impact of the campaign. These resources can be distributed at healthcare facilities, such as clinics and hospitals, or at other public environments such as schools, libraries etc.	
		Communication of practice	Yes	Improving the awareness and PV culture within the public, focusing on patients, can be achieved through community information projects. This can be done through training patient members of the public into the planning phase of the project to ensure the patients' needs can be addressed. Through involving the different stakeholders in the planning phase of the project (drug safety) one can help gaining knowledge on the topics to include in the educational campaign.	
		Collaboration & partnership	No	Collaboration and partnership with existing PV bodies, healthcare facilities and pharmaceutical companies can be an effective strategy to support with people and create awareness about PV with different stakeholders. Advancing efforts the importance of PV can be conducted by creating and sharing awareness with different stakeholders.	
		Providing Feedback	No	Providing feedback on the meeting or reports is important, however to create a culture of PV, some feedback should be provided to the reporter. This feedback system should be created that provide the reporter with additional information of the process to follow once a report has been received. This feedback system should also consider giving some form of a 'working' system of the report, to keep the reporter up to date, if they would wish to have more.	
Communication	In a PV system there are various stakeholders that play a vital role in the system. These interventions are needed to create, improve, enhance and maintain communication channels between the different stakeholders. Information about ADRs received and actions taken or considering to be implemented should be communicated to the different stakeholders to ensure transparency.	Education	No	Education of PV can improve the culture of reporting through capacity building.	
		Communication networks	Yes	Having that there is a proper communication network plan, that indicates the flow of information between the different stakeholders is vital. The communication network plan should provide an overview of the different communication channels that have to exist between the different stakeholders. Furthermore, the communication network plan should specify the flow of information and communication network used. The communication network needs to be designed specifically taking the project's needs into consideration.	
		Information communication technologies (ICT)		Information and Communication Technologies are technologies, primarily communication technologies such as internet, wireless and cellular networks, that use telecommunications to provide access to information. ICT can be an effective intervention and communication tool used by different stakeholders for different reasons. One reporting, giving feedback and information flow between the different stakeholders.	
		Email	Yes	Email people have access to email accounts, email communication is a very effective and commonly used form. Email groups can also be created between the different stakeholders to ensure transparency.	
		Conferences	No	Conferencing applications, like WhatsApp, are widely used in developing and developed countries for the purpose of communicating. Groups can be created for the purpose of communicating the necessary information to provide a lot of parties and for those in emergency help, such as understanding about important information.	
		Video-conferences	Yes	Video conferencing, such as Skype, is a platform form of communicating with different parties, often when a formal meeting or discussion is required.	
Education	The education component address the different interventions that can be implemented to improve capacity building in PV and ADR reporting. The educational interventions can be targeted at the different stakeholders or audience groups and focus not only on educating on the process of reporting but also on the importance of reporting.	Poster-based	Yes	In the environments where electronic forms of communication are not a viable option, poster-based communication settings need to be in place to ensure the information flows between the different stakeholders. Printed notices, newsletters and poster-based resources can be distributed using postal services.	
		Guidelines & Policies	Yes	Guidelines and policies can be used to improve communication between the different stakeholders. These guidelines should include a detailed description of the information flow that should exist within these communication plans.	
		Web-based	Yes	Web-based training and PV websites can be used to support PV education for different audience groups from BSA, to patients. These websites are seen as a platform that can link the user to e-learning services, articles and training materials, and training or workshops being held. Furthermore a website can be used as a platform to provide current news and information about pharmacovigilance and drug safety monitoring. Websites, such as Clinical Pharmacovigilance (http://clinicalpharmacovigilance.org) have proven to be a great resource for not only educational purposes but also for networking, creating awareness and providing information about current conferences and events.	
		Learning centres	No	The focus of learning centres are to create an open environment for collaboration, discussion and teaching opportunities on a non-pressured basis. The learning centres can serve as an environment for PV education through providing and facilitating workshops, training courses and collaboration with other PV bodies. Furthermore, these learning centres can be aimed at different target audience groups within the healthcare setting and different levels of PV experience. The training centres can be workshops aimed at students in the pharmaceutical and medical fields, conferences for experts in the field of PV or a course for all audience groups.	
		PV curriculum	No	The WHO in collaboration with International Society of Pharmacovigilance (ISoP) and the Education and Training Program (ETP) group developed the Pharmacovigilance Curriculum. The focus of this curriculum is to provide an overview of PV, provide information and training on new topics in PV and prepare a guide for the practice of PV. The curriculum contains the PV, clinical aspects of ADRs, role of various ADRs, quality of evidence, reporting methods, regulatory bodies, and communication. The PV curriculum has been developed in such a way that it can be adapted to the specific audience, environment and availability of time.	
		Patient information cards	Yes	Patient information cards on a paper-based method aimed at providing the patient with information regarding their specific treatment and possible ADRs. This card contains information on the symptoms of the adverse effects related to the specific drugs, how and when to report the ADRs. These information cards can be paper-based or electronic, depending on the patient.	
Quality management	In any system ensuring that proper quality management is integrated within the different systems are of the utmost importance. This is true for the development of a PV system as well. The concept of quality management should not only be addressed in the process of reporting and assessing ADRs but should also look at integrating with the drug manufacturing and distribution systems.	Workshops	No	The workshops are aimed at engaging different people in activities and discussion on PV and ADRs, much similar to learning centres. However, the workshops are more intense sessions that will occur on a small scale. As the workshops will be required to occur on a small scale, the specific PV topic, audience, and area will be determined on where the need is. Current PV workshops have been active in different areas around the world and online platforms. Materials resources can be shared through the ISoP PV curriculum and can be shared to address the needs and audience specific needs.	
		Short-courses	Yes	Short courses are intensive method of education that does not require an extensive amount of time and resources that can be used to acquire, update or enhance skills. PV short courses are aimed at setting a high level in a short amount of time. The short courses can be provided on an online platform or in a physical space such as at university or PV centres.	
		Social media platforms	No	When considering the different social media platforms and the focus of PV education, the social platforms to consider would be YouTube, using video education, and Twitter and LinkedIn for creating academic networks. Currently there are a vast number of videos available on YouTube that can be used to create an open environment for PV education. These videos are aimed at improving patient safety. These videos are aimed at PV workshops that a group intervention for educating patients. When considering the networking platforms, Twitter and LinkedIn, these platforms are used to share and distribute articles that are being published related to PV or some other literature in the PV domain.	
		Poster-based	Yes	Poster-based resources, such as pamphlets and posters, can be a very effective way of improving education on PV, ADRs and drug safety monitoring in BSA. Pamphlets and posters can be used to provide necessary and important information about the PV, the most useful tool for paper-based reporting ADRs. These poster-based educational resources can be aimed at different audience groups, however, would probably be the most effective educational resource for educating patients on PV.	
		GVP	No	The guidelines for GVP were published in 2013 by the ICH and are divided into two main chapters: pharmacovigilance processes and population and quality management. The guidelines provide an overview of all the relevant topics with regard to PV and drug safety. The guidelines provide best practice information about collection of the different reports, the validation and follow-up of the reports, and the dissemination process. Information of the use of evaluation during pregnancy and for paediatric and elderly also included.	
		Audio	Yes	Audio plays a vital role in ensuring the quality standards are met and as with any system PV system requires regular audits to be conducted. During a PV audit a number of investigations are conducted to ensure that all parts meet the required quality standards. The aim is to use the audit to evaluate the pharmacovigilance system and the effectiveness of the system. The audit results a review of the quality management of the collection, processing and management of the data system and ensuring if the standards meet the current regulations. The guidelines and rules and responsibilities of the personnel are also assessed.	
Responsibility & accountability	Responsibility and accountability are a key factor that relates to stakeholder involvement within a PV system. As there are multiple stakeholders involved within the PV system in that each stakeholder understands their specific role. Responsibility refers to an individual conducting and taking ownership of a specific task, whereas accountability refers to the taking on of a liability and answerability of a task. Thus, within a system one individual may be responsible for conducting a task, however the accountability lies with a different individual.	Policy & guidelines	Yes	To ensure that effective quality management is executed within the system a document plan which outlines the standard operating procedures should be developed. The document plan, policy, should ensure that the different stakeholders are clear about the different roles, responsibilities, and required task and the process for proper control and if and be changes are included.	
		Monitoring sectors	Yes	Throughout the different report and processes of the PV system quality management should be executed. The necessary collection and ensure that quality standards are met during the downstream, data collection, data transfer, management, or division and validation, and follow-up. Quality control guidelines need to be in place to ensure the data entry and the appropriate use of technology. Furthermore, the data that needs to be compared to the audit and follow-up data to ensure the integrity of the data. These different quality control checks need to be performed in a regular and systematic or systematically. These monitoring process and one should also be introduced to pharmacovigilance manufacturing companies where the drugs are manufactured.	
		Addressing GDP & GDP	No	As with GVP, guidelines for good manufacturing practices (GMP) and good distribution practices (GDP) have been developed by the WHO to ensure consistent quality standards are met in all aspects of drug manufacturing from material sourcing to the final product. These guidelines also consider drug safety monitoring aspects. The WHO guidelines include guidelines related to companies, product recall, quality audits, sampling and testing, which can be important to incorporate PV specific aspects.	
		PV stakeholder policy	Yes	For a system to be effective it is necessary that there is a policy that stipulates a high-level statement that provides information about the overarching aim of the system. Furthermore, the policy needs to clearly define the roles, responsibilities and accountability of the different stakeholders involved. The policy needs to ensure the required actions called for by the stakeholders and be linked to the different standards, procedures and guidelines. Therefore, the stakeholder policy should provide the framework for the operational process to follow the policy and guidelines to ensure general communication would. The PV stakeholder policy refers to the development of a policy for a specific PV system that will define the roles and responsibilities of the stakeholders within the specific system. The WHO has set up a PV policy that can be used as a guideline to help to set a policy related to the stakeholder's roles for a PV system.	
		Designated PV persons	No	Having a designated number of staff that specifically relate on the role of accountability of ADR reporting within the healthcare facility would not only drive the workload of the DCP but will also address the concept of accountability as there would be a specific group individual that takes on all aspects of PV. Depending on the availability of resources and the size of the healthcare facility the size of the designated PV department can be determined. The department's main focus as mentioned would be to report ADRs to the National PV centre and provide necessary feedback when needed. As the department would be responsible for all PV related reports, the target of staff in the reporting process will be critical and the process of follow-up would be easier. Furthermore, this concept of designated PV departments can also be introduced to pharmaceutical manufacturing companies to improve the communication, coordination, and responsibility of pharmaceutical manufacturing companies with the PV centres and healthcare facilities.	
Incentives Schemes	In the healthcare landscape incentive schemes have become an emerging strategy in various fields and targeted at a range of DCP. Incentive strategies that are designed for the specific context and environment in which they will be implemented are found to be more successful. Incentives are a strategy to ensure practitioners and healthcare bodies to develop and sustain a desired workload.	Financial incentives	Yes	There are three main financial incentives categories namely bonus, wages and conditions, performance-related payments, and three additional financial incentives. The first category, bonus, wages and conditions, refers to ensuring the level of wage paid and an incentive and for when compared to other colleagues. Offering a basic level of compensation is a key element to ensuring a satisfied workforce. The second category, performance-related incentives refers to additional payments or bonuses. These forms of incentives are aimed to promote a culture of commitment of care and to ensure better experienced workforces. However, paid or not, according to the state of the healthcare and are linked to the individual's work performance or professional development. The third category, additional financial services, are related to healthcare or outside the working, support and other services.	
		Career & performance development	Yes	Incentives such as access to education programs and training, effective mentoring and supervision can contribute to a supportive approach to continuous development. Through providing educational and development opportunities individuals improve their professional development which allows their ability to function and other benefits.	
		Workload management	Yes	As the healthcare landscape, heavy workload has a major concern that contributes to low satisfaction, poor performance or ultimately leaving the healthcare profession. Most of these factors that contribute to heavy workload are the shortage of workers, inefficient staff, or a rise in increased demand. However, there are possible methods that can be implemented to address heavy workload. Firstly, incorporating temporary resources for staff as a compensation for working overtime and overtime for employees to improve workload management. Secondly, scheduling additional hours or time-in-line is another form of staff. Another possible method is to create rotating roles and responsibilities to improve workload distribution among the different staff members. Finally, the number of continuous working hours related to staff members should be regulated to prevent patient safety.	
		Flexible working arrangements	Yes	These initiatives look at accommodating workers to encourage effective working methods. These incentives include providing arrangements to allow flexible hours of work, increased leave arrangements or arrangements for staff members that are balancing their work with their other commitments like family life. Furthermore, these initiatives should also include introducing arrangements that allow older staff to stay employed but with less intensive working hours and conditions, such as a part-time role or a role of education.	
		Positive working environments	Yes	Ensuring a positive working environment through creating a positive organizational culture and staff working environment are crucial factors for increasing staff numbers and improving staff satisfaction. Factors to consider incorporating are decentralized organizational structure, flexible working hours, and effective communication between management and staff. Incorporating these factors can improve the working environment by improving morale of staff members.	
		Benefits & support	Yes	Although financial incentives are not always a possibility there are other support incentives that can be offered and provided. Such as providing housing, transport and food. Also providing centres for childcare to employee support.	

Figure H.1: Case B customised vigilance implementation strategy

Appendix I. Validation questionnaires

In this appendix additional information regarding the verification process of the tool is provided. This information includes the pre-read documents and questionnaires used during the validation.

I1 Pre read document

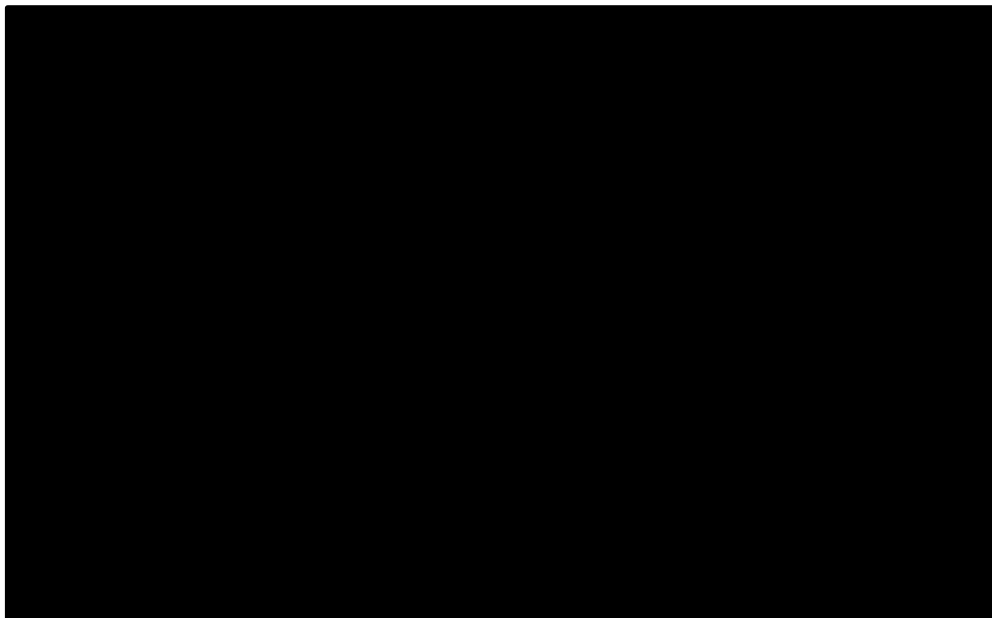
I2 - questionnaire

I.1.Pre-read document for validation process

Innovative Pharmacovigilance: **Towards a vigilance system** *CVIT application pre-read document*

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1. Introduction

In the modern-day health landscape, there has been a significant change within the pharmaceutical industry with regards to innovative drug manufacturing and distribution systems which calls for improved surveillance and monitoring systems that can support such systems. One such an innovation is the Medicine Patent Pool (MPP)¹ which aims to improve access to affordable drugs for TB, HIV and Hepatitis C in low- and middle-income countries [1].

However it is often the case that these provision systems are deployed in areas that do not have effective 'PV systems'² for the reporting of adverse drug reactions (ADRs) and face the challenge of being implemented in resource limited settings (RLS) [2]. The fact that numerous manufacturers could be utilised through the MPP to generate drugs, intensifies the need to monitor drug quality and once again highlights the need for effective drug safety monitoring and PV systems within this context.

All these factors reaffirm the need for more innovative PV systems to be implemented that will address these niche specific factors. Thus, the aim of this research investigation is to propose a vigilance system, through the development of a conceptual framework and decision

¹ The MPP is a public health organisation that was launched in 2010 by UNITAID and aims to improve accessibility and development of life-saving drugs for HIV, TB, and hepatitis C in developing countries through the sharing of technologies and patents [1]. The MPP collaborates closely with industry stakeholders and patent holders to develop licence agreements which allow pharmaceutical companies to manufacture generic versions of drugs, as well as with the World Health Organisation to prioritise these drugs for licensing [4]. Through this innovative drugs are made available to a broader population at a faster rate [4]. In addition to having drugs provided to a broader population through the implementation of the MPP, there are additional advantages such as encouraging research and development and facilitating competition [3], [5], [6].

² as, "the science and activities relating to the related problem"

supporting tool, that will support the effective and efficient reporting of ADR's for pilot drug roll-out projects in RLS.

It was decided that a system engineering approach would be used, as this approach transforms an operational need into a system solution by breaking down the need into smaller comprehensible parts to address [3]. Using this approach the Vigilance System Framework was created along with the Customised Vigilance Implementation Tool (CVIT). This tool is a decision support tool that assists pilot drug roll-out projects with creating a implementation strategy for a drug safety monitoring system best suited for the project under consideration.

The focus of this validation is to reaffirm the operationality, functionality and validity of the CVIT through applying a illustrative case study on the roll-out of Bedaquiline in south Africa. The operations of the CVIT, background on the Bedaquiline case study, and findings from applying the CVIT to the case will be provided in this document.

2. Customised Vigilance Implementation Tool (CVIT) operations

As mentioned CVIT aims to assist projects with the development of customised implementation strategy for a vigilance system. The CVIT was developed from the Vigilance System Implementation Framework, which provides an overview of direct components, supporting components and additional factors that have to be addressed when setting up a vigilance system. These components are listed in Table 1. Each of these components have a subsequent list of intervention strategies that can be implemented to address these components.

The focus of the CVIT is to identify which intervention strategies are best suited to the project based on the project's background, patient profile, and human and technology resource availability. Using the data a vigilance profile can be created for the project which gets mapped against the different intervention strategies. Using a potential mapping function the applicable intervention strategies are identified and provided to the user. These intervention strategies can then be investigated further to determine the financial, technical and operational feasibility with regards to the specific project under consideration.

Table 1: Vigilance System Framework components

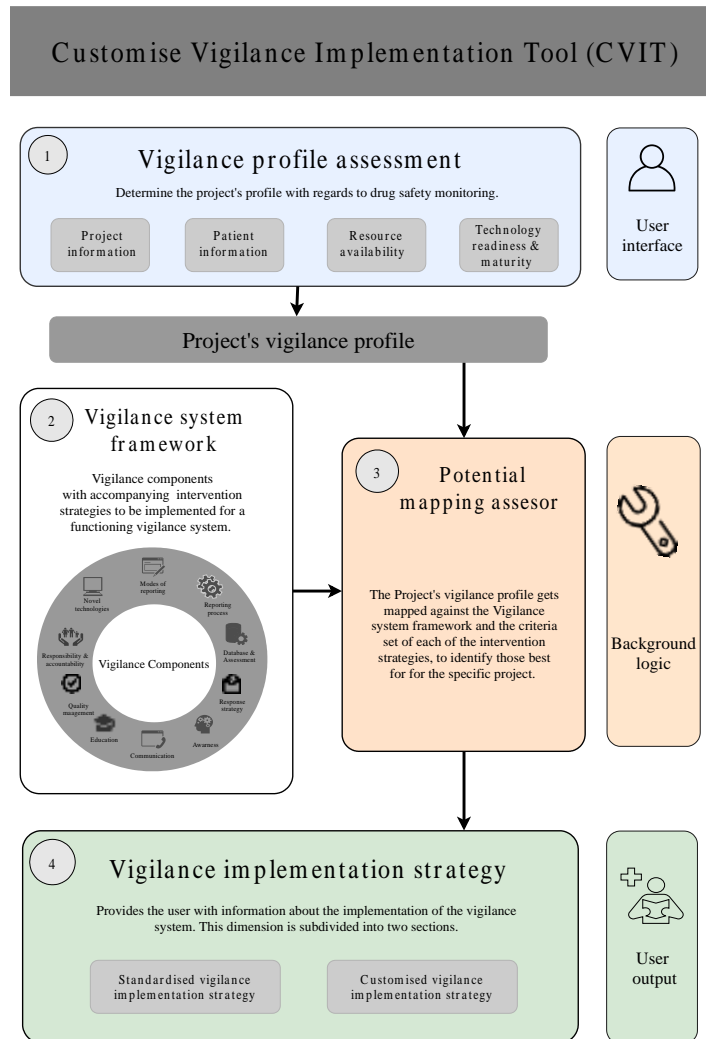
Component Group	Components
Direct Components	Modes of reporting
	Reporting process
	Databases
	Response strategy
Sporting Components	Awareness
	Communication
	Education
	Quality management
	Responsibility & Accountability
Additional Factors	Novel technologies

2.1. Dimensions of the CVIT

project's unique

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strategy provides the user with an overview of the different vigilance components that need to be implemented for an effective vigilance system as well as the different intervention strategies that address each of these vigilance components. The second section, the customised vigilance implementation strategy builds on the previous section as it provides the user with the implementation strategies best fit for the specific project, as determined from the vigilance profile.



2.2. Operation of CVIT

3. References

- [1] Medicine Patent Pool, “Who We Are – MPP.” [Online]. Available: <https://medicinespatentpool.org/who-we-are/>. [Accessed: 15-Nov-2018].
- [2] E. Burrone, “Global Cooperation for IP and Development - presentation.” Medicine Patent Pool.
- [3] Department of Defense - System Managemnet Collegue, “SYSTEMS ENGINEERING,” Virgina - USA, 2001.
- [4] MPP, “What We Do – MPP.” [Online]. Available: <https://medicinespatentpool.org/what-we-do/>. [Accessed: 21-May-2018].
- [5] Medicine Patent Pool, “The Medicines Patent Pool Stimulating Innovation, Improving Access,” Geneva, Switzerland, 2011.
- [6] R. B. Taylor *et al.*, “The UNITAID Patent Pool Initiative: Bringing Patents Together for the Common Good,” *Open AIDS J.*, vol. 2, no. 2, pp. 214–219, 2011.

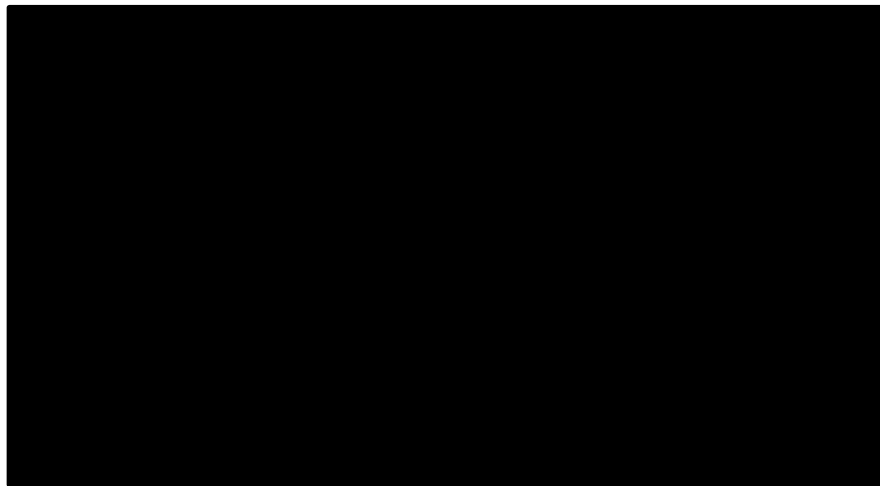
I.2.Pre-read document for validation process

Innovative Pharmacovigilance: Towards a vigilance system

Questionnaire

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Introduction

No	Question	Likert Scale rating				
		<i>Strongly disagree</i>	<i>Disagree</i>	<i>Neutral</i>	<i>Agree</i>	<i>Strongly agree</i>
1	To what extent do you agree that the CVIT provides a systematic and holistic approach of an implementation strategy for a vigilance system.					
<i>Additional comments related to question 1</i>						
2	Considering the case study, to what extent do you agree that the CVIT allows for the consideration of different components not necessarily direct related to drug safety monitoring?					
<i>Additional comments related to question 2</i>						
3	Considering the terminology and operability please rate the CVIT in terms of ease of use and intuitive to understand.					
<i>Additional comments related to question 3</i>						

No	Question	Likert Scale rating				
		<i>Strongly disagree</i>	<i>Disagree</i>	<i>Neutral</i>	<i>Agree</i>	<i>Strongly agree</i>
4	To what extent do you agree that the user of the tool does not require a very high level of experience or knowledge on drug safety monitoring and pharmacovigilance.					
<i>Additional comments related to question 4</i>						
5	To what extent do you agree that the CVIT is more widely applicable than the attended use. In other words, to what extent do you agree that the CVIT could be applicable to any existing drug project, and not only pilot drug roll-out projects?					
<i>Additional comments related to question 5</i>						
6	What do you view as some of the key strengths of the CVIT?					
7	What do you view as some of the key weaknesses of the CVIT?					

No	Question	Likert Scale rating				
		<i>Strongly disagree</i>	<i>Disagree</i>	<i>Neutral</i>	<i>Agree</i>	<i>Strongly agree</i>
8	Are you aware of any other system or decision-making tool or framework with which the CVIT could complimentary be used with?					